SEARCH REQUEST FORM

Requestor's Name: Janice Li

Serial Number: 09/586,535

Date: 2/25/02

Phone: ~~703~~ 703-308-7942

Art Unit: 1632

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Structrue search for the cationic lipid formular of claim 12, particularly when it is used together with a genetic vaccine construct (DNA vaccine), more particularly with a pocine pathogenic vaccine.

Inventors: Jean Christopher

Claim 12 is enclosed P.D. -

GB

pre?

Point of Contact:
Susan Hanley
Technical Info. Specialist
CM1 12C14 Tel: 305-4053

4785
f4785

L1

2/26

STAFF USE ONLY

Date completed: 3/6/02

Searcher: Hanley

Terminal time:

Elapsed time:

CPU time:

Search Site

_____ STIC

_____ CM-1

_____ Pre-S

Type of Search

Vendors

_____ IG

_____ STN

_____ Dialog

_____ APS

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=> d his

     (FILE 'HOME' ENTERED AT 10:10:24 ON 06 MAR 2002)

     FILE 'HCAPLUS' ENTERED AT 10:10:38 ON 06 MAR 2002
L1            43 S AUDONNET J?/AU
L2            32 S BUBLOT M?/AU
L3          1848 S PEREZ J?/AU
L4             6 S CHARREYRE C?/AU
L5          1912 S L1-4
L6            53 S L5 AND VACCINE
L7             4 S L6 AND QUAT?
L8          1764 S CATION?(2A)LIPID
L9             4 S L8 AND L5
L10            5 S L7 OR L9
                 SELECT RN L10 1-5

     FILE 'REGISTRY' ENTERED AT 10:14:37 ON 06 MAR 2002
L11          200 S E1-200
L12           60 S E201-260
L13          260 S L11-12
L14            6 S L13 AND N/ELS

     FILE 'HCAPLUS' ENTERED AT 10:16:23 ON 06 MAR 2002
L15            5 S L14 AND L10

     FILE 'REGISTRY' ENTERED AT 10:19:09 ON 06 MAR 2002
L16              STR
L17            1 S L16
L18              STR L16
L19            0 S L18
L20              SCREEN 2040 AND 1992 AND 2004
L21            1 S L18 AND L20
L22           40 S L18 AND L20 FUL
                 SAVE L22 LI535P/A

     FILE 'HCAPLUS' ENTERED AT 10:29:10 ON 06 MAR 2002
L23          154 S L22
L24          149 S L23 NOT L10
L25       209929 S PORCINE OR PIG
L26            4 S L25 AND L24
L27      1350407 S ?VIRUS? OR ?VIRAL OR NUCLEIC OR DNA OR GENE OR GENETIC
L28        53117 S PCV(W)1 OR PCV(W)2 OR VACCIN?
L29            4 S L26 AND L27-28
L30          145 S L24 NOT L29
L31          137 S L30 AND L27-28
L32           14 S L31 AND VACCIN?
L33          123 S L31 NOT L32
L34           56 S L33 AND PATENT/DT
L35           67 S L33 NOT L34
L36           47 S L35 AND PD<19990610
L37            3 S L36 AND IMMUNOGEN?
L38            9 S L36 AND IMMUN?
L39            9 S L37-38

     FILE 'USPATFULL' ENTERED AT 11:47:31 ON 06 MAR 2002
L40           36 S L22
L41        37971 S PORCIN? OR PIG
L42            9 S L40 AND L41
L43         1080 S PCV
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inventor search

date X

5 cites w/ 6 compounds displayed

40 cpds from full search

154 citations for L22 cpds

14 cites related to porcine

14 cites related to vaccines in general

9 cites related to immun? and cite & applns Pub date pr. date

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=> d que l23
L18             STR
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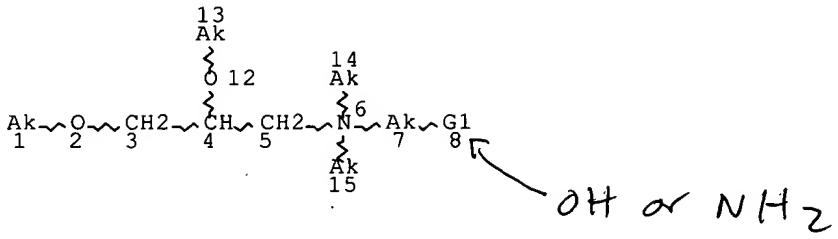
Ak = alkyl

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CONNECT IS E1  RC AT  13
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CONNECT IS E1  RC AT  15
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GGCAT   IS LIN  AT  13
GGCAT   IS LIN  SAT  AT  14
GGCAT   IS LIN  SAT  AT  15
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ECOUNT  IS M10 C  AT   1
ECOUNT  IS M2-X6 C  AT   7
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ECOUNT  IS X5 C  AT  14
ECOUNT  IS X5 C  AT  15

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  12

STEREO ATTRIBUTES: NONE
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L23         154 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22
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40 cpd s

=> d ibib abs hitstr 1

L15 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10302 HCAPLUS
DOCUMENT NUMBER: 136:74555
TITLE: **Vaccine** against foot-and-mouth disease
INVENTOR(S): King, Andrew; Burman, Alison; **Audonnet, Jean-Christophe**; Lombard, Michel
PATENT ASSIGNEE(S): Merial, Fr.
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000251	A1	20020103	WO 2001-FR2042	20010627
FR 2810888	A1	20020104	FR 2000-8437	20000629

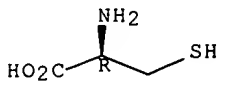
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: FR 2000-8437 A 20000629
OTHER SOURCE(S): MARPAT 136:74555

AB The invention concerns a **vaccine** against foot-and-mouth disease, using as antigen an efficient amt. of empty capsids of the foot-and-mouth virus, said empty capsids being obtained by expressing, in eukaryotic cells, cDNA of the P1 region of the foot-and-mouth virus genome coding for the capsid and cDNA of the region of the foot-and-mouth virus genome coding for protease 3C, the **vaccine** further comprising a carrier or excipient pharmaceutically acceptable in veterinary medicine. The invention also concerns the insertion of a mutation in the sequence VP2 (introducing a cysteine), thereby stabilizing the empty capsids and the resulting viruses.

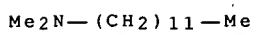
IT **52-90-4**, Cysteine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(codon for; **vaccine** against foot-and-mouth disease)
RN 52-90-4 HCAPLUS
CN L-Cysteine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

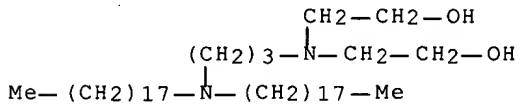


IT **112-18-5**, Dda **35607-20-6**, Avridine
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**vaccine** against foot-and-mouth disease)
RN 112-18-5 HCAPLUS

CN 1-Dodecanamine, N,N-dimethyl- (9CI) (CA INDEX NAME)



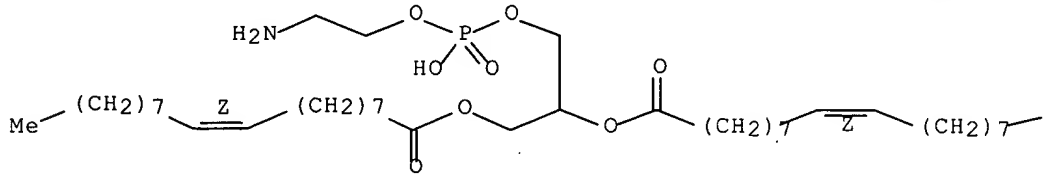
RN 35607-20-6 HCAPLUS
CN Ethanol, 2,2'-[[3-(dioctadecylamino)propyl]imino]bis- (9CI) (CA INDEX NAME)



IT **2462-63-7**, Dope **153312-64-2**, Dmrie
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**vaccine** against foot-and-mouth disease)
RN 2462-63-7 HCAPLUS
CN 9-Octadecenoic acid (9Z)-, 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl ester (9CI) (CA INDEX NAME)

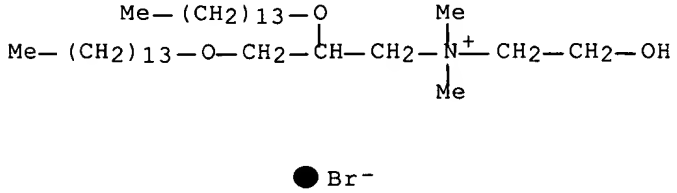
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d ibib abs hitstr 2

L15  ANSWER 2 OF 5  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:545519  HCAPLUS
DOCUMENT NUMBER:          135:142202
TITLE:                    Improved DNA vaccines for livestock
INVENTOR(S):              Audonnet, Jean-Christophe Francis; Fischer,
                          Laurent Bernard; Barzu-le-Roux, Simona
PATENT ASSIGNEE(S):       Merial, Fr.
SOURCE:                   PCT Int. Appl., 79 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 French
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     WO 2001052888      A2   20010726      WO 2001-FR187    20010119
     WO 2001052888      A3   20011220
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
              CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
              HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
              LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
              SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
              ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
          RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
              DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
              BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     FR 2804028         A1   20010727      FR 2000-798      20000121
PRIORITY APPLN. INFO.:                   FR 2000-798      A  20000121
OTHER SOURCE(S):           MARPAT 135:142202
AB   The invention concerns a DNA vaccine against a pathogen
     affecting livestock, in particular cattle and swine, comprising a plasmid
     contg. a nucleotide sequence coding for an immunogen of a pathogen of the
     animal species concerned, in conditions enabling the expression in vivo of
     said sequence, and a cationic lipid contg. a
     quaternary ammonium salt, of formula R1-O-CH2-CH(OR1)-CH2-N+(CH3)2-
     R2 X-, wherein: R1 is a linear aliph. radical, satd. or unsatd., having 12
     to 18 carbon atoms; R2 is another aliph. radical, contg. 2 or 3 carbon
     atoms; and X is a hydroxyl or amine group, said lipid being preferably
     DMRIE.
IT   2462-63-7, Dope 153312-64-2, Dmrie
     RL: PEP (Physical, engineering or chemical process); THU (Therapeutic
     use); BIOL (Biological study); PROC (Process); USES (Uses)
        (improved DNA vaccines for livestock)
RN   2462-63-7  HCAPLUS
CN   9-Octadecenoic acid (9Z)-, 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methy
     l]-1,2-ethanediyl ester (9CI)  (CA INDEX NAME)

Double bond geometry as shown.
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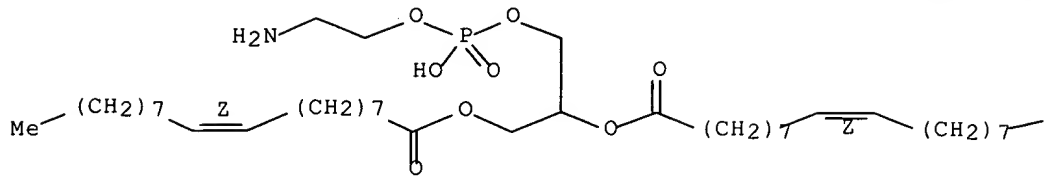
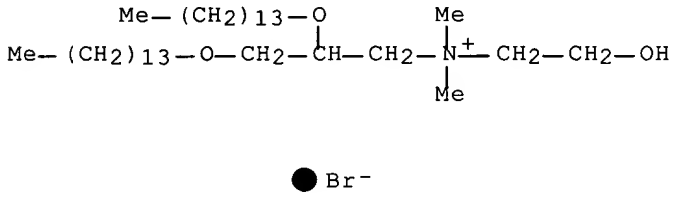
PAGE 1-A



PAGE 1-B

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 3

L15 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:64121 HCAPLUS
DOCUMENT NUMBER: 134:136654
TITLE: Feline calicivirus genes and **vaccines**, in particular recombined **vaccines**
INVENTOR(S): **Audonnet, Jean-Christophe Francis**; Baudu, Philippe Guy Nicolas; Brunet, Sylvie Claudine
PATENT ASSIGNEE(S): Merial, Fr.
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005934	A2	20010125	WO 2000-FR2051	20000713
WO 2001005934	A3	20010426		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2796396	A1	20010119	FR 1999-9421	19990716
FR 2796397	A1	20010119	FR 2000-1761	20000211
AU 2000065765	A5	20010205	AU 2000-65765	20000713

PRIORITY APPLN. INFO.:
FR 1999-9421 A 19990716
FR 2000-1761 A 20000211
WO 2000-FR2051 W 20000713

OTHER SOURCE(S): MARPAT 134:136654

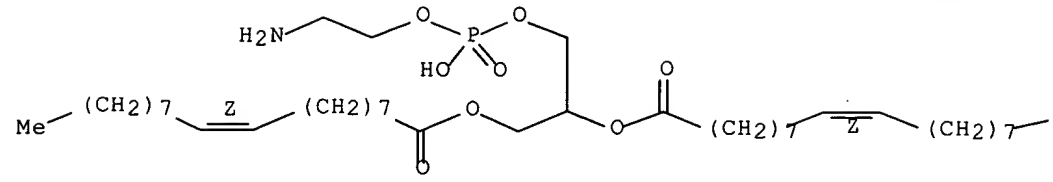
AB The invention concerns the sequence of the capsid gene and a corresponding cDNA sequence, of a dominant FCV strain called FCV 431. The invention also concerns the capsid gene sequence and the cDNA sequence of a complementary strain called G1. The cDNA sequences can be incorporated in expression vectors for prepg. immunogenic formulations and recombined **vaccines** or subunits providing vaccination against the feline calicivirus disease.

IT **2462-63-7**, Dope **153312-64-2**, Dmrie
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(adjuvant; feline calicivirus genes and **vaccines**)

RN 2462-63-7 HCAPLUS
CN 9-Octadecenoic acid (9Z)-, 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl ester (9CI) (CA INDEX NAME)

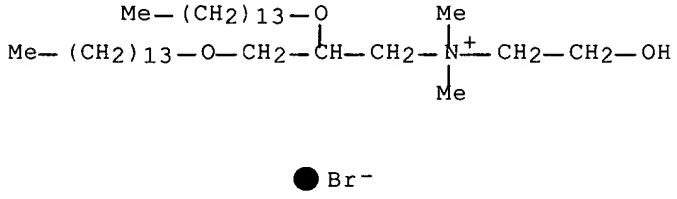
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 4

L15 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:900790 HCAPLUS
DOCUMENT NUMBER: 134:55493
TITLE: Porcine circovirus vaccine
INVENTOR(S): **Audonnet, Jean-christophe Francis; Bublot, Michel; Perez, Jennifer Maria ; Charreyre, Catherine Elisabeth**
PATENT ASSIGNEE(S): Merial, Fr.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000077188	A2	20001221	WO 2000-EP5611	20000608
WO 2000077188	A3	20010531		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

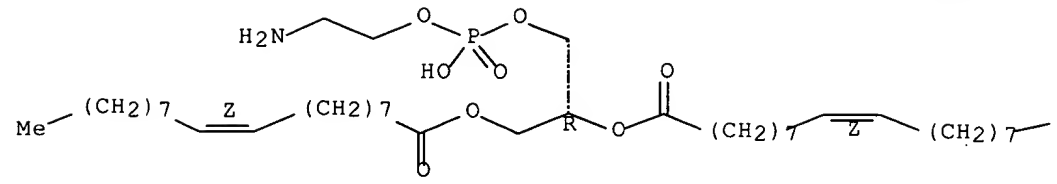
PRIORITY APPLN. INFO.: US 1999-138352 P 19990610
OTHER SOURCE(S): MARPAT 134:55493

AB The invention relates to immunogenic prepns. or vaccines comprising, on the one hand, a plasmid vector encoding and expressing a gene from porcine circovirus (PCV), in particular selected from the group consisting of ORF1 of PCV-2, ORF2 of PCV-2, ORF1 of PCV-1 and ORF2 of PCV-1, and , on the other hand, an element capable of increasing the immune response directed against the product of expression of the gene, which can be a carbomer, a porcine cytokine, e.g. GM-CSF or a **cationic lipid** of formula (I), in which R1 is a satd. or unsatd. linear aliph. radical having from 12 to 18 carbon atoms, R2 is another aliph. radical comprising from 2 to 3 carbon atoms, and X is a hydroxyle or amine group. The **cationic lipid** can be DMRIE, possibly coupled with DOPE. Vaccines contg. plasmid vector encoding and expressing a gene from porcine circovirus were prepd. and tested against PMWS.

IT **4004-05-1**, DOPE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vaccine comprising DMRIE coupled to; porcine circovirus vaccine)
RN 4004-05-1 HCAPLUS
CN 9-Octadecenoic acid (9Z)-, (1R)-1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy] methyl]-1,2-ethanediyl ester (9CI) (CA INDEX NAME)

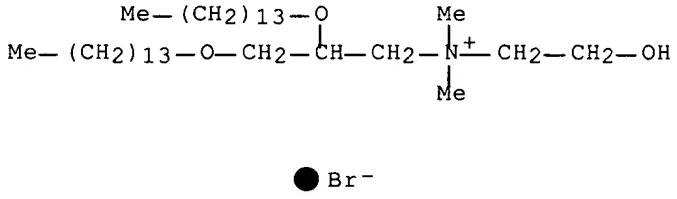
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

IT **153312-64-2**, DMRIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vaccine comprising, **cationic lipid** or neutral lipid; porcine circovirus vaccine)
RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 5

L15 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:900679 HCAPLUS
DOCUMENT NUMBER: 134:55491
TITLE: DNA **vaccines** against Paramyxoviridae for pets and game animals and their delivery in liposomes containing **cationic lipids**
INVENTOR(S): Fischer, Laurent Jean-Charles; Barzu-le, Roux Simona; **Audonnet, Jean-Christophe Francis**
PATENT ASSIGNEE(S): Merial, Fr.
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000077043	A2	20001221	WO 2000-FR1592	20000608
WO 2000077043	A3	20010719		

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FR 2794648	A1	20001215	FR 1999-7604	19990610

PRIORITY APPLN. INFO.: FR 1999-7604 A 19990610
US 1999-144490 P 19990719
OTHER SOURCE(S): MARPAT 134:55491

AB The invention aims at improving the efficacy and protection induced by DNA vaccination against viruses of the family of Paramyxoviridae and against the herpes virus, in pets and sport animals. The improvement of DNA vaccination is achieved either by formulating the **vaccine** with a **cationic lipid** contg. a **quaternary** ammonium salt, DMRIE, or by modifications in the nucleotide sequence coding for the antigen of interest in particular of deletions of the fragment of the nucleotide sequence coding for the transmembrane domain of the antigen of interest, and/or insertions of introns and/or insertions of nucleotide sequences coding for the signal peptides, or by adding GM-CSF, or by combinations thereof. The invention also concerns the resulting **vaccines**. A series of expression vectors for antigen genes of canine distemper virus and felid, canid, and equid herpes viruses that used the signal sequence of a tissue plasminogen activator gene were constructed by std. methods. In some cases, derivs. lacking the transmembrane domain were used to improve secretion of the extracellular domain. Expression vectors also carrying the genes for cytokines, esp. colony-stimulating factor 2 were also constructed. Use of genes for colony-stimulating factor 2 derived from the target host is demonstrated. A combination of vectors carrying genes for the fusion protein and hemagglutinin of canine distemper virus completely protected a group of five dogs challenged with the virus.

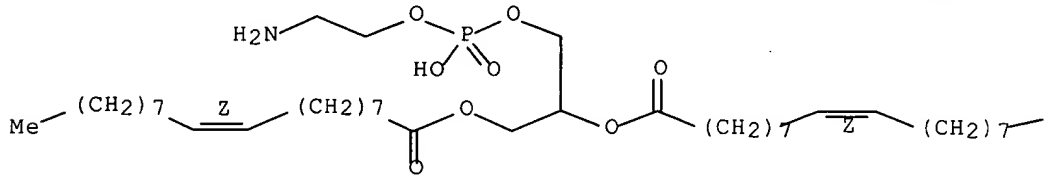
IT **2462-63-7**, DOPE **153312-64-2**, DMRIE

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in liposomes for delivery of DNA **vaccines**; DNA **vaccines** against Paramyxoviridae for pets and game animals and their delivery in liposomes contg. **cationic lipids**)

RN 2462-63-7 HCAPLUS
CN 9-Octadecenoic acid (9Z)-, 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl ester (9CI) (CA INDEX NAME)

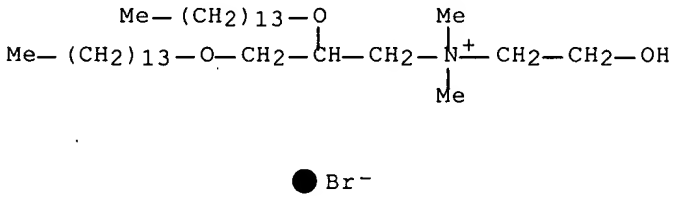
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 1

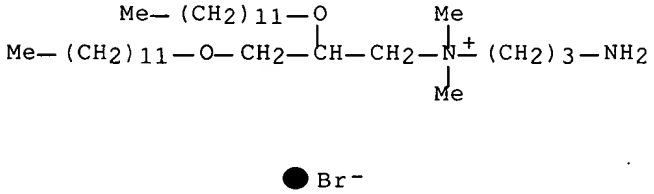
L29 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:791879 HCAPLUS
DOCUMENT NUMBER: 135:335117
TITLE: Immunological adjuvants containing Hemagglutinating **virus**-containing charged liposomes, and manufacture thereof
INVENTOR(S): Honda, Kazuo; Kaneda, Yasushi; Shiozaki, Koichi
PATENT ASSIGNEE(S): Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001302541	A2	20011031	JP 2000-128670	20000428

AB The invention relates to an immunol. adjuvant having immunostimulating effect for low-immunogenic peptide, wherein the adjuvant is a charged liposome consisting of a Sendai **virus** (Hemagglutinating **virus** of Japan, HVJ **virus**) or its envelop glycoprotein, and a lipid component. A HIV-V3 peptide-contg. anionic liposome was prepd. from dimethylaminoethane carbamyl cholesterol, phosphatidylethanolamine, egg yolk phosphatidylcholine, cholesterol, inactivated HVJ **virus**, and HIV-V3 peptide, and its booster effect was examd. in guinea **pigs** primarily immunized with HIV-HBc (hepatitis B **virus** core antigen).

IT **182919-20-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(charged liposomes contg. Hemagglutinating **virus** and lipids as immunol. adjuvants)

RN 182919-20-6 HCAPLUS
CN 1-Propanaminium, N-(3-aminopropyl)-2,3-bis(dodecyloxy)-N,N-dimethyl-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 2

L29 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:168152 HCAPLUS
DOCUMENT NUMBER: 134:221435
TITLE: Prevention of myocarditis, abortion and intrauterine infection associated with **porcine circovirus**-2
INVENTOR(S): Ellis, John Albert; Allan, Gordon Moore; Meehan, Brian; Clark, Edward; Haines, Deborah; Hassard, Lori; Harding, John; Charreyre, Catherine Elisabeth; Chappuis, Gilles Emile; Krakowka, George Steve; Audonnet, Jean-Christophe Francis; McNeilly, Francis
PATENT ASSIGNEE(S): Merial, Fr.; University of Saskatchewan; The Queen's University of Belfast
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016330	A2	20010308	WO 2000-EP8781	20000828

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

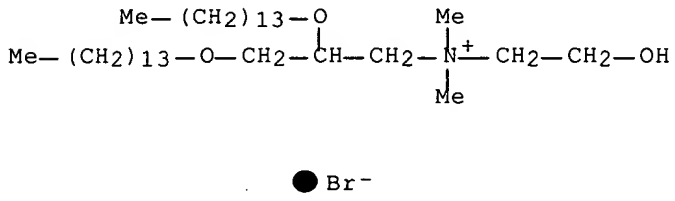
PRIORITY APPLN. INFO.: US 1999-151564 P 19990831
US 2000-583350 A 20000531

AB The invention is based on the discovery that **porcine circovirus** (**PCV-2**) is a causative agent of myocarditis, abortion and intrauterine infection, as well as post-weaning multisystemic wasting syndrome in **pigs**. Thus, immunol. compns. contg. the recombinant **poxvirus** for inducing an immunol. response in aa host animal to which the immunol. compn. is administered. Also described are methods of treating or preventing disease caused by **PCV-2** by administering the immunol. compns. of the invention to an animal in need of treatment or susceptible to infection by **PCV-2**. Such immunol. compns. comprise (1) attenuated or inactivated strains of **PCV-2**, (2) plasmid vectors expressing open reading frames of **PCV-2** and **vaccination** of **pigs** with **DNA** formulated with DMRIE, DMRIE-DOPE, or carbomer adjuvants, and (3) a recombinant **poxvirus**, such as the canarypox **virus** (Rentschler strain) contg. foreign **DNA** encoding the major capsid **virus** or ORF1 or ORF2 from **PCV-2**.

IT **153312-64-2**, DMRIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvant; prevention of myocarditis, abortion and intrauterine infection assocd. with **porcine circovirus**-2)

RN 153312-64-2 HCAPLUS

CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



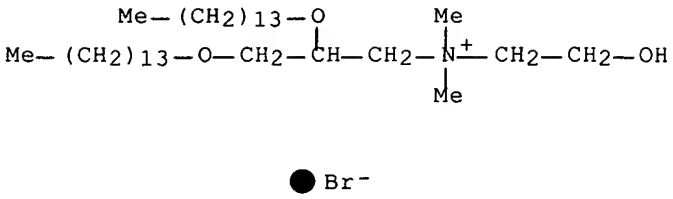
=> d ibib abs hitstr 3

L29 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:654418 HCAPLUS
DOCUMENT NUMBER: 125:338808
TITLE: A new cationic liposome **DNA** complex enhances the efficiency of arterial **gene** transfer in vivo
AUTHOR(S): Stephan, Dominique J.; Yang, Zhi-Yong; San, Hong; Simari, Robert D.; Wheeler, Carl J.; Felgner, Philip L.; Gordon, David; Nabel, Gary J.; Nabel, Elizabeth G.
CORPORATE SOURCE: Department Internal Medicine, University Michigan, Ann Arbor, MI, 48109-0644, USA
SOURCE: Hum. Gene Ther. (1996), 7(15), 1803-1812
CODEN: HGTHE3; ISSN: 1043-0342
DOCUMENT TYPE: Journal
LANGUAGE: English

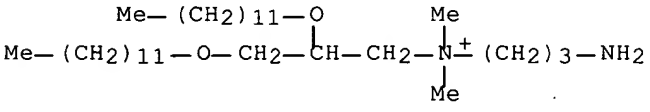
AB An important goal of **gene** therapy for cardiovascular diseases and cancer is the development of effective vectors for catheter-based **gene** delivery. Although **adenoviral** vectors have proven effective for this purpose in animal models, the ability to achieve comparable **gene** transfer with **nonviral** vectors would provide potentially desirable safety and toxicity features for clin. studies. In this report, we describe the use of a new cationic **DNA**-liposome complex using an improved expression vector and lipid, N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(dodecyloxy)-1-propaniminium bromide/dioleoyl phosphatidylethanolamine (GAP-DL-RIE/DOPE) to optimize catheter-mediated **gene** transfer in **porcine** arteries. The efficiency of this vector was compared to **DNA** alone, **DNA** with a previously described cationic liposome complex, (.+-.)-N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide (DMRIE/DOPE), and a replication-defective **adenoviral** vector in a **porcine** artery **gene** transfer model. When used in optimal ratios, GAP-DL-RIE/DOPE liposomes provided a 15-fold higher level of **gene** expression in arteries compared to **DNA** alone or DMRIE/DOPE. **Gene** expression was obsd. in intimal and medial cells. However, when compared to **adenoviral** vectors (1010 pfu/mL), **gene** expression following GAP-DL-RIE/DOPE transfection was .apprx.20-fold lower. Following i.v. injection of GAP-DL-RIE/DOPE in mice, biochem., hematol., and histopathol. abnormalities were not obsd. Significant improvements in the efficacy of arterial **gene** expression can be achieved by optimization of transfection conditions with **DNA**-liposome complexes in vivo that may prove useful for arterial **gene** delivery in cardiovascular diseases and cancer.

IT **153312-64-2 182919-20-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic liposome/**DNA** complexes for arterial **gene** transfer in cardiovascular diseases and cancer)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



RN 182919-20-6 HCAPLUS
CN 1-Propanaminium, N-(3-aminopropyl)-2,3-bis(dodecyloxy)-N,N-dimethyl-, bromide (9CI) (CA INDEX NAME)



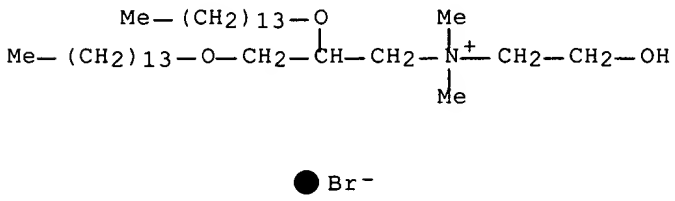
=> d ibib abs hitstr 4

L29 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:236112 HCAPLUS
DOCUMENT NUMBER: 120:236112
TITLE: Safety and short-term toxicity of a novel cationic lipid formulation for human **gene** therapy
AUTHOR(S): San, Hong; Yang, Zhi Yong; Pompili, Vincent J.; Jaffe, Michele L.; Plautz, Gregory E.; Xu, Ling; Felgner, Jiin H.; Wheeler, Carl J.; Felgner, Philip L.; et al.
CORPORATE SOURCE: Med. Cent., Univ. Michigan, Ann Arbor, MI, 48109-0650, USA
SOURCE: Hum. Gene Ther. (1993), 4(6), 781-8
CODEN: HGTHE3; ISSN: 1043-0342
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Among the potential **nonviral** vectors for human **gene** therapy are **DNA**-liposome complexes. In a recent clin. study, this delivery system has been utilized. In this report, a novel cationic lipid, dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium (DMRIE), has been substituted into the **DNA**-liposome complex with dioleoyl phosphatidylethanolamine (DOPE), which both improves transfection efficiencies and allows increased doses of **DNA** to be delivered in vivo. The safety and toxicity of this **DNA**-liposome complex has been evaluated in two species, mice and **pigs**. The efficacy of DMRIE/DOPE in inducing an antitumor response in mice after transfer of a foreign MHC has been confirmed. No abnormalities were detected after administration of .ltoreq.1,000-fold higher concns. of **DNA** and lipid than could be tolerated in vivo previously. Examn. of serum biochem. enzymes, pathol. examn. of tissue, and anal. of cardiac function in mice and **pigs** revealed no toxicities related to this treatment. This improved cationic lipid formulation is well-tolerated in vivo and could therefore allow higher dose administration and potentially greater efficiency of **gene** transfer for **gene** therapy.

IT **153312-64-2**
RL: BIOL (Biological study)
(liposomes contg., for **gene** therapy, efficacy and toxicity of)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 1

L32 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:798084 HCAPLUS
DOCUMENT NUMBER: 135:348865
TITLE: Compositions and methods for in vivo delivery of polynucleotide-based therapeutics
INVENTOR(S): Hartikka, Jukka; Sukhu, Loretta; Manthorpe, Marston
PATENT ASSIGNEE(S): Vical Incorporated, USA
SOURCE: PCT Int. Appl., 176 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

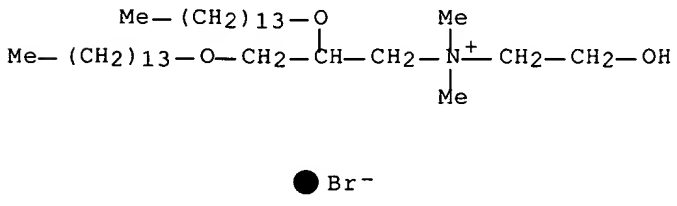
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080897	A2	20011101	WO 2001-US12975	20010423
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 2002019358	A1	20020214	US 2001-839574	20010423

PRIORITY APPLN. INFO.: US 2000-198823 P 20000421
US 2000-253153 P 20001128

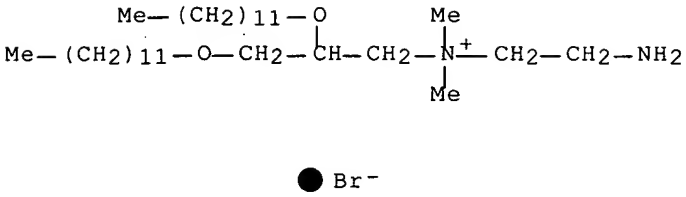
AB The present invention relates to pharmaceutical compns. and methods to improve expression of exogenous polypeptides into vertebrate cells in vivo, utilizing delivery of polynucleotides encoding such polypeptides. More particularly, the present invention provides the use of salts, in particular sodium and potassium salts of phosphate, in aq. soln., and auxiliary agents, in particular detergents and surfactants, in pharmaceutical compns. and methods useful for direct polynucleotide-based polypeptide delivery into the cells of vertebrates.

IT **153312-64-2**, Dmrie **208040-06-6**, Gap dlrie
299207-54-8, Gap-dmorie
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(compns. and methods for in vivo delivery of polynucleotide-based therapeutics)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)

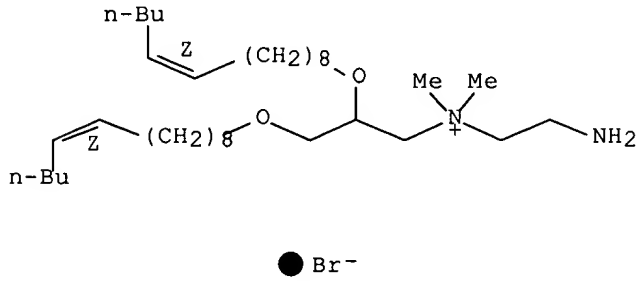


RN 208040-06-6 HCAPLUS
CN 1-Propanaminium, N-(2-aminoethyl)-2,3-bis(dodecyloxy)-N,N-dimethyl-, bromide (9CI) (CA INDEX NAME)



RN 299207-54-8 HCAPLUS
CN 1-Propanaminium, N-(2-aminoethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



=> d ibib abs hitstr 2

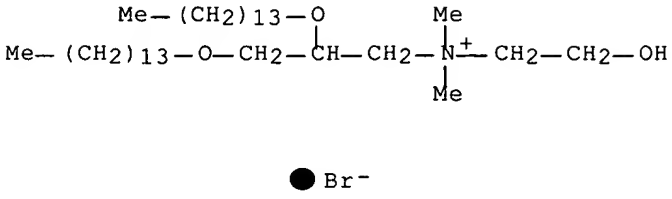
L32 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:490587 HCAPLUS
DOCUMENT NUMBER: 135:362424
TITLE: Highly efficient **gene** delivery by mRNA electroporation in human hematopoietic cells: superiority to lipofection and passive pulsing of mRNA and to electroporation of plasmid cDNA for tumor antigen loading of dendritic cells
AUTHOR(S): Van Tendeloo, Viggo F. I.; Ponsaerts, Peter; Lardon, Filip; Nijs, Griet; Lenjou, Marc; Van Broeckhoven, Christine; Van Bockstaele, Dirk R.; Berneman, Zwi N.
CORPORATE SOURCE: Laboratory of Experimental Hematology, Antwerp University Hospital, University of Antwerp, Antwerp, Belg.
SOURCE: Blood (2001), 98(1), 49-56
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Designing effective strategies to load human dendritic cells (DCs) with tumor antigens is a challenging approach for DC-based tumor **vaccines**. Here, a cytoplasmic expression system based on mRNA electroporation to efficiently introduce tumor antigens into DCs is described. Preliminary expts. in K562 cells using an enhanced green fluorescent protein (EGFP) reporter **gene** revealed that mRNA electroporation as compared with plasmid **DNA** electroporation showed a markedly improved transfection efficiency (89% vs. 40% EGFP+ cells, resp.) and induced a strikingly lower cell toxicity (15% death rate with mRNA vs. 51% with plasmid **DNA**). Next, mRNA elec. troporation was applied for **nonviral** transfection of different types of human DCs, including monocyte-derived DCs (Mo-DCs), CD34+ progenitor-derived DCs (34-DCs) and Langerhans cells (34-LCs). High-level transgene expression by mRNA electroporation was obtained in more than 50% of all DC types. MRNA-electroporated DCs retained their phenotype and maturational potential. Importantly, DCs electroporated with mRNA-encoding Melan-A strongly activated a Melan-A-specific cytotoxic T lymphocyte (CTL) clone in an HLA-restricted manner and were superior to mRNA-lipofected or -pulsed DCs. Optimal stimulation of the CTL occurred when Mo-DCs underwent maturation following mRNA transfection. Strikingly, a nonspecific stimulation of CTL was obsd. when DCs were transfected with plasmid **DNA**. The data clearly demonstrate that Mo-DCs electroporated with mRNA efficiently present functional antigenic peptides to cytotoxic T cells. Therefore, electroporation of mRNA-encoding tumor antigens is a powerful technique to charge human dendritic cells with tumor antigens and could serve applications in future DC-based tumor **vaccines**.

IT **189203-05-2**, DMRIE-C
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipofection with; highly efficient **gene** delivery by mRNA electroporation in human hematopoietic cells for tumor antigen loading of dendritic cells)
RN 189203-05-2 HCAPLUS
CN Cholest-5-en-3-ol (3.beta.)-, mixt. with N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide (9CI) (CA INDEX NAME)

CM 1

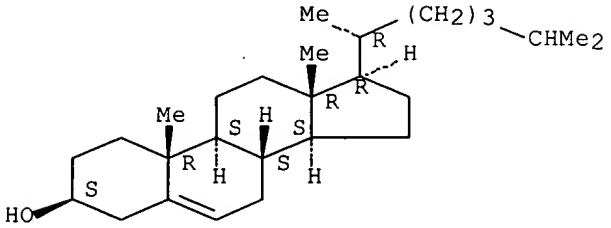
CRN 153312-64-2
CMF C35 H74 N O3 . Br



CM 2

CRN 57-88-5
CMF C27 H46 O
CDES 4:3B.CHOLEST

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 3

L32 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:167832 HCAPLUS
DOCUMENT NUMBER: 134:212748
TITLE: Lipid-**nucleic** acid compositions for stimulating cytokine secretion and inducing an immune response
INVENTOR(S): Semple, Sean C.; Harasym, Troy O.; Klimuk, Sandra K.; Kojic, Ljiljiana D.; Bramson, Jonathan L.; Mui, Barbara; Hope, Michael J.
PATENT ASSIGNEE(S): Inex Pharmaceuticals Corp., Can.
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001015726	A2	20010308	WO 2000-CA1013	20000828
WO 2001015726	A3	20010726		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-176406 P 20000113

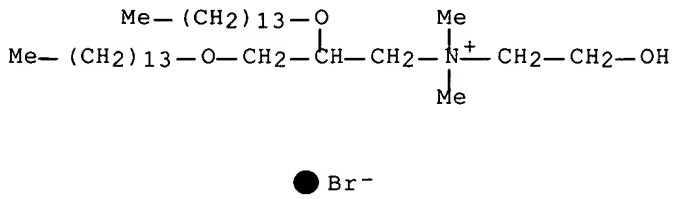
AB Lipid-**nucleic** acid particles can provide therapeutic benefits, even when the **nucleic** acid is not complementary to coding sequences in target cells. It has been found that lipid-**nucleic** acid particles, including those contg. non-sequence specific oligodeoxynucleotides, can be used to stimulate cytokine secretion, thus enhancing the overall immune response of a treated mammal. Further, immune response to specific target antigens can be induced by administration of an antigenic mol. in assocn. with lipid particles contg. non-sequence specific oligodeoxynucleotides. The **nucleic** acid which is included in the lipid-**nucleic** acid particle can be a phosphodiester (i.e., an oligodeoxynucleotide consisting of nucleotide residues joined by phosphodiester linkages) or a modified **nucleic** acid which includes phosphorothioate or other modified linkages, and may suitably be one which is non-complementary to the human genome, such that it acts to provide immunostimulation in a manner which is independent of conventional base-pairing interactions between the **nucleic** acid and **nucleic** acids of the treated mammal. In particular, the **nucleic** acid may suitably contain an immune-stimulating motif such as a CpG motif, or an immune stimulating palindromic sequence. The cationic lipid included in the **nucleic** acid particles may be suitably selected from among DODAP, DODMA, DMDMA, DOTAP, DC-Chol, DDAB, DODAC, DMRIE, DOSPA and DOGS. In addn., the lipid particle may suitably contain a modified aggregation-limiting lipid such as a PEG-lipid, a PAO-lipid or a ganglioside.

IT **153312-64-2**, DMRIE

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(lipid-**nucleic** acid compns. for stimulating cytokine secretion and inducing an immune response)

RN 153312-64-2 HCAPLUS

CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



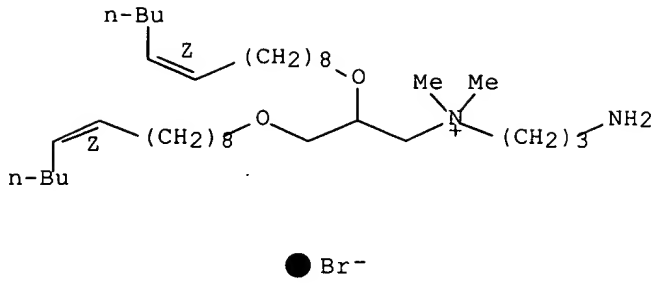
=> d ibib abs hitstr 4

L32 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:146642 HCAPLUS
DOCUMENT NUMBER: 135:330213
TITLE: Vaxfectin enhances the humoral immune response to plasmid **DNA**-encoded antigens
AUTHOR(S): Hartikka, J.; Bozoukova, V.; Ferrari, M.; Sukhu, L.; Enas, J.; Sawdey, M.; Wloch, M. K.; Tonsky, K.; Norman, J.; Manthorpe, M.; Wheeler, C. J.
CORPORATE SOURCE: Department of Cell Biology, Vical Incorporated, San Diego, CA, 92121, USA
SOURCE: Vaccine (2001), 19(15-16), 1911-1923
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This report characterizes Vaxfectin, a novel cationic and neutral lipid formulation which enhances antibody responses when complexed with an antigen-encoding plasmid **DNA** (pDNA). In mice, i.m. injection of Vaxfectin formulated with pDNA encoding influenza nucleoprotein (NP) increased antibody titers .ltoreq. 20-fold, to levels that could not be reached with pDNA alone. As little as 1 .mu.g of pDNA formulated with Vaxfectin per muscle resulted in higher anti-NP titers than that obtained with 25 .mu.g naked pDNA. The antibody titers in animals injected with Vaxfectin-pDNA remained higher than in the naked pDNA controls for at least 9 mo. The enhancement in antibody titers was dependent on the Vaxfectin dose and was accomplished without diminishing the strong anti-NP cytolytic T cell response typical of pDNA-based **vaccines**. In rabbits, complexing pDNA with Vaxfectin enhanced antibody titers .ltoreq. 50-fold with needle and syringe injections and also augmented humoral responses when combined with a needle-free injection device. Vaxfectin did not facilitate transfection and/or increase synthesis of .beta.-galactosidase reporter protein in muscle tissue. ELISPOT assays performed on bone marrow cells from **vaccinated** mice showed that Vaxfectin produced a 3- to 5-fold increase in the no. of NP-specific plasma cells. Thus, Vaxfectin should be a useful adjuvant for enhancing pDNA-based **vaccinations**.
IT **370108-99-9P**, Vaxfectin
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Vaxfectin enhances the humoral immune response to plasmid **DNA** -encoded antigens)
RN 370108-99-9 HCAPLUS
CN 1-Propanaminium, N-(3-aminopropyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide, mixt. with (1R)-1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl bis(3,7,11,15-tetramethylhexadecanoate) (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 370108-98-8
CMF C36 H73 N2 O2 . Br

Double bond geometry as shown.

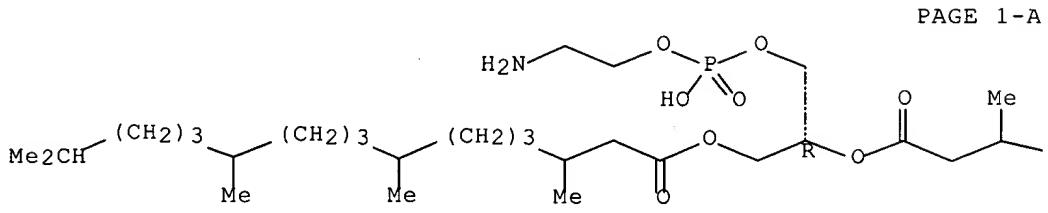


CM 2

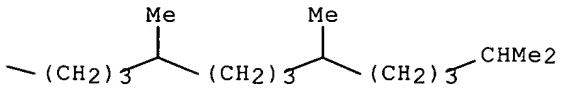
CRN 201036-16-0
CMF C45 H90 N O8 P

Absolute stereochemistry.

PAGE 1-A

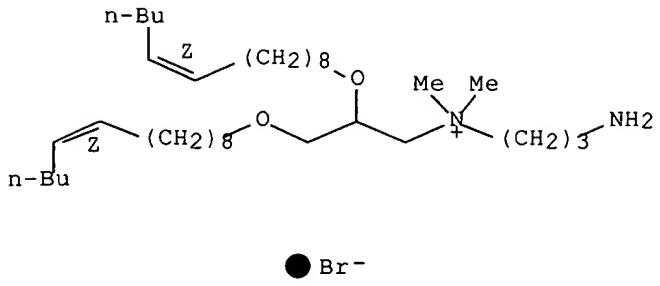


PAGE 1-B



IT **370108-98-8P**, VC 1052
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Vaxfectin enhances the humoral immune response to plasmid **DNA** -encoded antigens)
RN 370108-98-8 HCAPLUS
CN 1-Propanaminium, N-(3-aminopropyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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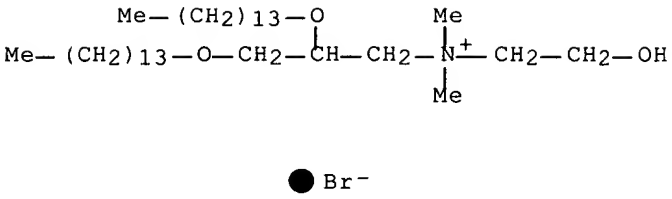
=> d ibib abs hitstr 5

L32  ANSWER 5 OF 14  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:114958  HCAPLUS
DOCUMENT NUMBER:          134:168319
TITLE:                    Periodic structures comprising lipids,
                          polyelectrolytes, and structure-inducing soluble
                          oligovalent linkers, and biological use thereof
INVENTOR(S):              Cevc, Gregor; Huebner, Stefan
PATENT ASSIGNEE(S):       Idea Ag, Germany
SOURCE:                   PCT Int. Appl., 33 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2001010413      A2   20010215       WO 2000-EP7546    20000803
     WO 2001010413      A3   20010816
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    DE 1999-19936665 A  19990804
AB   This invention describes a method for prepg. pharmaceutically usable
     compns. comprising periodic structures consisting of polyelectrolytes
     sandwiched between lipid aggregates having at least one charged component
     which is characterized in that a suspension of non-periodic, preferably
     mono- or bilayer like, lipid aggregates, a soln. of polyelectrolyte mols.,
     and a soln. of oligovalent linkers are sep. made and then mixed to form
     said periodic structures, the simultaneous presence of said components
     catalyzing the formation of controlling the rate of formation of said
     periodic structures comprising at least one layer of lipid component
     assocd. with a layer of polyelectrolyte mols.
IT   153312-64-2, Dmrie
     RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU
     (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
        (periodic structures comprising lipids, polyelectrolytes, and
        structure-inducing sol. oligovalent linkers, and biol. use thereof)
RN   153312-64-2  HCAPLUS
CN   1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-,
     bromide (9CI)  (CA INDEX NAME)
```



=> d ibib abs hitstr 6

L32 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:101291 HCAPLUS
DOCUMENT NUMBER: 134:161880
TITLE: cDNAs encoding the Flt-3 receptor ligand and there use as adjuvants in vector **vaccines**
INVENTOR(S): Hermanson, Gary George
PATENT ASSIGNEE(S): Vical Inc., USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001009303	A2	20010208	WO 2000-US20679	20000731
WO 2001009303	A3	20010816		

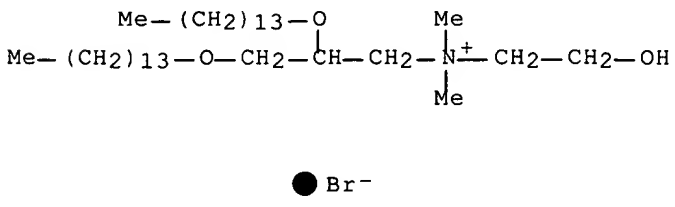
W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-146170 P 19990730

AB A method of increasing the strength of the immune response of vector **vaccines** using an expression vector for the Flt3 ligand is described. The **vaccines** are made of independent non-integrating expression vectors: one encodes the antigen or a cytokine and the other encodes the Flt3 ligand. The present invention also provides a method broadly directed to improving immune response of a vertebrate in need of immunotherapy by administering in vivo, into a tissue of a vertebrate, a Flt-3 ligand-encoding polynucleotide and one or more antigen- or cytokine-encoding polynucleotides. The polynucleotides are incorporated into the cells of the vertebrate in vivo, and a prophylactically or therapeutically effective amt. of a Flt-3 ligand and one or more antigens is produced in vivo.

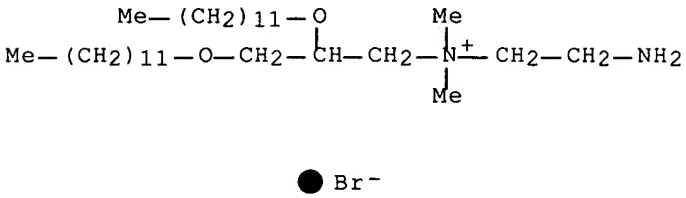
IT **153312-64-2**, DMRIE **208040-06-6**, GAP-DLRIE
299207-54-8, GAP-DMORIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in delivery of vector **vaccines**; cDNAs encoding Flt-3 receptor ligand and there use as adjuvants in vector **vaccines**)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



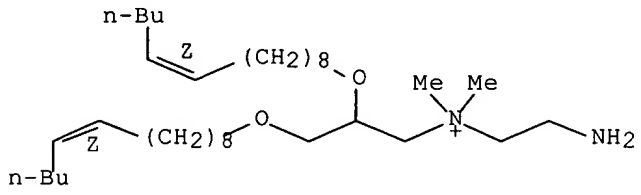
RN 208040-06-6 HCAPLUS

CN 1-Propanaminium, N-(2-aminoethyl)-2,3-bis(dodecyloxy)-N,N-dimethyl-, bromide (9CI) (CA INDEX NAME)



RN 299207-54-8 HCAPLUS
CN 1-Propanaminium, N-(2-aminoethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



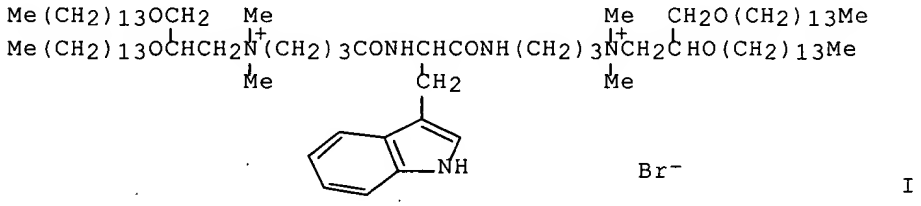
=> d ibib abs hitstr 7

L32 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:861646 HCAPLUS
DOCUMENT NUMBER: 134:21482
TITLE: Cytofectin dimers and methods of use thereof
INVENTOR(S): Wheeler, Carl J.
PATENT ASSIGNEE(S): Vical, Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073263	A1	20001207	WO 2000-US14676	20000526

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-136472 P 19990528
OTHER SOURCE(S): MARPAT 134:21482
GI

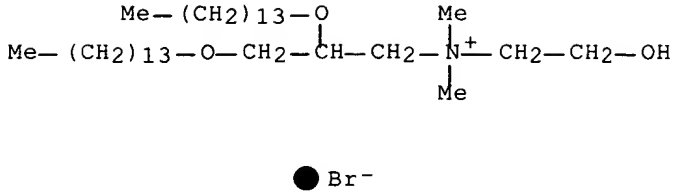


I

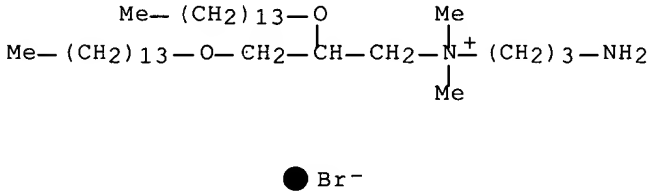
AB A compn. is provided comprising a novel cationic lipid compd. having hydrophobic tails and two quaternary ammonium headgroups bridged by a linker. The compn. is useful as a cytofectin for facilitating delivery and transfection of biol. active agents, particularly anionic bioactive agents such as **DNA**, into cells. The compn. is useful also as an adjuvant for enhancing the humoral immune response of a vertebrate to an immunogen, esp. an immunogen encoded by a polynucleotide-based **vaccine**. In certain preferred embodiments, the cationic lipid compd. is a dimer contg. quaternary ammonium headgroups bridged by a linker having **DNA** and/or cell receptor binding affinity, such as a polypeptide or polyamine. Also disclosed is an immunogenic compn. comprising an immunogen and the compn. of the present invention. I was prepd. as an example compd.

IT **153312-64-2**, Dmrie
RL: RCT (Reactant); RACT (Reactant or reagent)
(cationic lipids prepn. as cytofectin for delivery and transfection of biol. agents)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



IT **282533-25-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cationic lipids prepn. as cytofectin for delivery and transfection of biol. agents)
RN 282533-25-9 HCAPLUS
CN 1-Propanaminium, N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d ibib abs hitstr 8

L32  ANSWER 8 OF 14  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2000:707018  HCAPLUS
DOCUMENT NUMBER:         133:280556
TITLE:                   Adjuvant compositions and methods for enhancing immune
                         responses to polynucleotide-based vaccines
INVENTOR(S):             Wheeler, Carl J.
PATENT ASSIGNEE(S):      Vical Incorporated, USA
SOURCE:                  PCT Int. Appl., 72 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     WO 2000057917      A2   20001005      WO 2000-US8282   20000324
     WO 2000057917      A3   20010104
         W:  CA, JP, US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
     EP 1165140         A2   20020102      EP 2000-919777   20000324
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
PRIORITY APPLN. INFO.:                  US 1999-126340   P  19990326
                                        WO 2000-US8282  W  20000324
AB   The invention provides adjuvants, immunogenic compns., and methods useful
     for polynucleotide-based vaccination and immune response.  In
     particular, the invention provides an adjuvant of cytofectin:co-lipid
     mixt. wherein cytofectin is GAP-DMORIE.
IT   153312-60-8, DORIE 153312-64-2, DMRIE
     154486-25-6, GAP-DMRIE 188949-12-4, DMORIE
     199171-54-5, DLRIE 208040-06-6, GAP-DLRIE
     299207-53-7, DDRIE 299207-54-8, GAP-DMORIE
     299207-55-9, GAP-DPRIE
     RL: BAC (Biological activity or effector, except adverse); PEP (Physical,
     engineering or chemical process); THU (Therapeutic use); BIOL (Biological
     study); PROC (Process); USES (Uses)
        (adjuvant compns. contg. cytofectin:co-lipid mixts. and methods for
        enhancing immune responses to polynucleotide-based vaccines)
RN   153312-60-8  HCAPLUS
CN   1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-
     octadecenyloxy]-, bromide (9CI)  (CA INDEX NAME)

Double bond geometry as shown.
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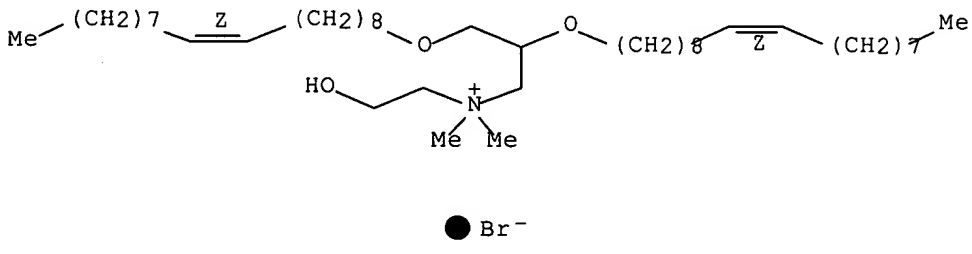

RN 153312-64-2 HCAPLUS
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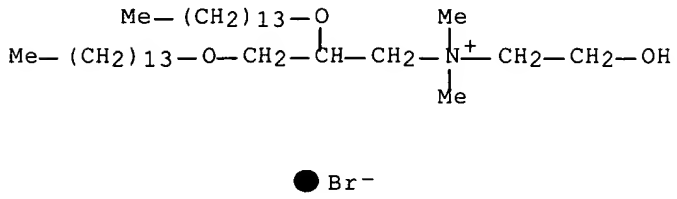

RN 154486-25-6 HCAPLUS
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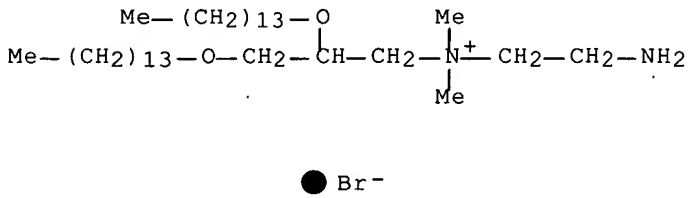
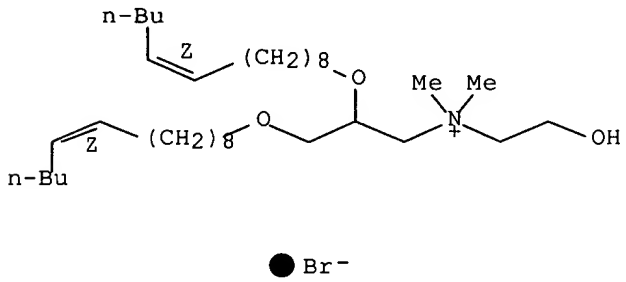


RN 188949-12-4 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 199171-54-5 HCAPLUS
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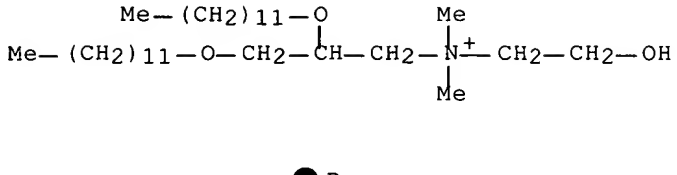

● Br^-

RN 208040-06-6 HCAPLUS
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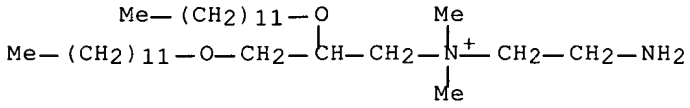
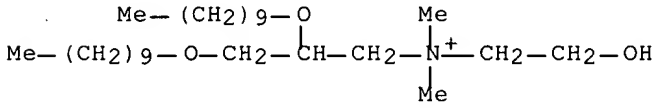


● Br^-

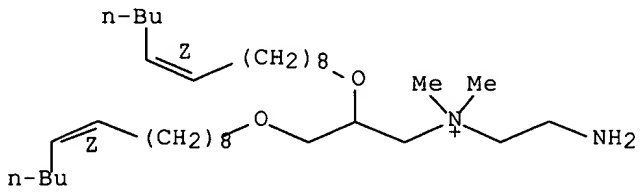
RN 299207-53-7 HCAPLUS
CN 1-Propanaminium, 2,3-bis(decyloxy)-N-(2-hydroxyethyl)-N,N-dimethyl-, bromide (9CI) (CA INDEX NAME)



● Br^-

RN 299207-54-8 HCAPLUS
CN 1-Propanaminium, N-(2-aminoethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● Br^-

RN 299207-55-9 HCAPLUS
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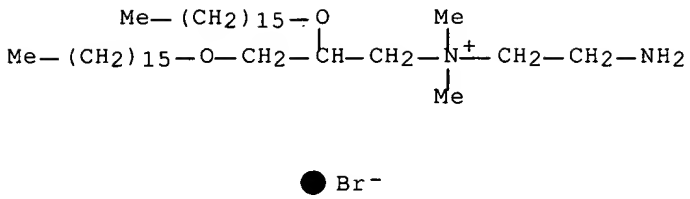
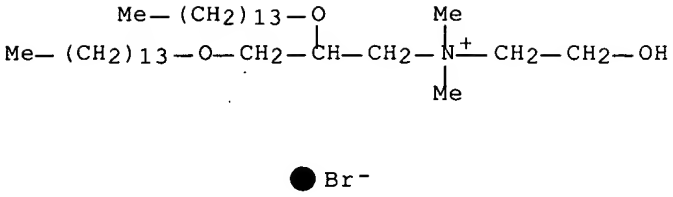


=> d ibib abs hitstr 9

L32 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:648161 HCAPLUS
DOCUMENT NUMBER: 133:308810
TITLE: Transfected human dendritic cells to induce antitumor immunity
AUTHOR(S): Rughetti, A.; Biffoni, M.; Sabbatucci, M.; Rahimi, H.; Pellicciotta, I.; Fattorossi, A.; Pierelli, L.; Scambia, G.; Lavitrano, M.; Frati, L.; Nuti, M.
CORPORATE SOURCE: Department of Experimental Medicine and Pathology, Universita di Roma 'La Sapienza', Rome, 00161, Italy
SOURCE: Gene Ther. (2000), 7(17), 1458-1466
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dendritic cells are professional antigen-presenting cells able to prime naive T lymphocytes and regulate steadily the delicate balance between tolerance and activation during the immune response. In past years several reports have shown that genetically engineered dendritic cells (DCs) can be a powerful tool for inducing an antigen-specific immune response. The use of such modified antigen-presenting cells is a real working hypothesis in preclin. studies and in clin. **vaccination** approaches for cancer treatment. The definition of optimal transfection conditions for preserving DC survival and functionality is necessary to design a correct immunotherapeutic protocol. Different lipid-based transfection compds. were studied for their effects on DC survival, phenotype and functional properties. All the transfection procedures were able to select DCs with a higher expression of activation and costimulatory mols. (ie MHCII-DR, CD83, CD86, CD25) than the untreated DCs. However, only two compds. (LipofectAMINE PLUS and FuGENE 6), preserved or even increased the immunopotency of DCs as antigen-presenting cells. These protocols were applied to modify DCs to express an epithelial tumor-assocd. antigen, MUC1, and such cells were able to induce in vitro a specific immune response in healthy donors.
IT **189203-05-2**, DMRIE-C
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect of transfection agents on phenotype, function, and survival of dendritic cells)
RN 189203-05-2 HCAPLUS
CN Cholest-5-en-3-ol (3.beta.)-, mixt. with N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide (9CI) (CA INDEX NAME)

CM 1

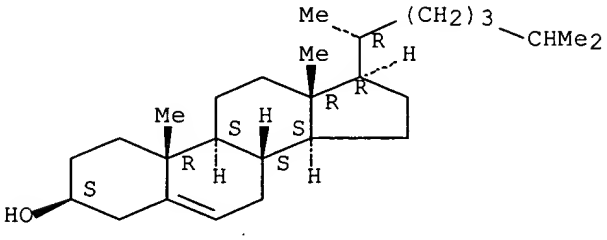
CRN 153312-64-2
CMF C35 H74 N O3 . Br



CM 2

CRN 57-88-5
CMF C27 H46 O
CDES 4:3B.CHOLEST

Absolute stereochemistry.



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

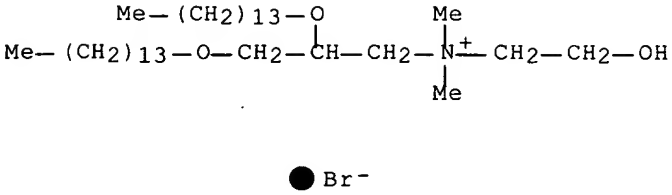
=> d ibib abs hitstr 10

L32 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:573482 HCAPLUS
DOCUMENT NUMBER: 134:146025
TITLE: Effectiveness of combined interleukin 2 and B7.1 **vaccination** strategy is dependent on the sequence and order: A liposome-mediated **gene** therapy treatment for bladder cancer
AUTHOR(S): Larchian, William A.; Horiguchi, Yutaka; Nair, Smita K.; Fair, William R.; Heston, Warren D. W.; Gilboa, Eli
CORPORATE SOURCE: Department of Urology, The Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: Clinical Cancer Research (2000), 6(7), 2913-2920
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have developed a novel liposome-mediated immunogene therapy using interleukin 2 (IL-2) and B7.1 in a murine bladder cancer model. A carcinogen-induced murine bladder cancer cell line, MBT-2, was transfected with cationic liposome 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide/dioleolylphosphatidylethanolamine and IL-2 plasmid. The optimized transfection condition generated IL-2 levels of 245-305 ng/106 cells/24 h, 100-fold higher than the levels seen with **retrovirus** transfection. Ninety percent of the peak level of IL-2 prodn. was maintained for up to 11 days after transfection. Animal studies were conducted in C3H/HeJ female mice with 2.times.104 MBT-2 cells implanted orthotopically on day 0. Multiple **vaccination** schedules were performed with i.p. injection of 5.times.106 IL-2 and/or B7.1 **gene** -modified cell prepns. The greatest impact on survival was obsd. with the day 5, 10, and 15 regimen. Control animals receiving retrovirally **gene**-modified MBT-2/IL-2 cell prepns. had a median survival of 29 days. Animals receiving the IL-2 liposomally **gene**-modified cell prepn. alone had a median survival of 46 days. Seventy-five percent of animals receiving IL-2 followed by B7.1 **gene**-modified tumor **vaccines** were the only group to show complete tumor-free survival at day 60. All of these surviving animals rejected the parental MBT-2 tumor rechallenge and survived at day 120 with a high CTL response. Thus, liposome-mediated transfection demonstrates a clear advantage as compared with the **retroviral** system in the MBT-2 model. Multi-agent as opposed to single-agent cytokine **gene**-modified tumor **vaccines** were beneficial. These "targeted" sequential **vaccinations** using IL-2 followed by B7.1 **gene**-modified tumor cells increased a systemic immune response that translated into increased survival.

IT **153312-64-2**, DMRIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposome contg.; combined interleukin 2 and B7.1 **vaccination** strategy in liposome-mediated **gene** therapy of bladder cancer is dependent on sequence and order)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

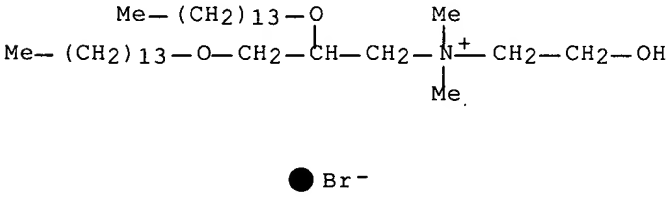
=> d ibib abs hitstr 11

L32 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:679109 HCAPLUS
DOCUMENT NUMBER: 132:164839
TITLE: Adjuvants for plasmid **DNA vaccines**
AUTHOR(S): Norman, Jon; Hartikka, Jukka; Strauch, Pamela; Manthorpe, Marston
CORPORATE SOURCE: Vical Inc., San Diego, CA, USA
SOURCE: Methods Mol. Med. (2000), 29, 185-196
CODEN: MMMEFN
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 38 refs. discussing the effects of the co-injection of bupivacaine (BP), polyvinyl pyrollidone (PVP), or DMRIE:DOPE cationic liposomes on plasmid **DNA**-mediated luciferase **gene** expression and antibody responses to influenza nucleoprotein (NP) antigen.

IT **153312-64-2**, DMRIE
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DMRIE/DOPE liposomes contg.; adjuvants for plasmid **DNA vaccines**)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

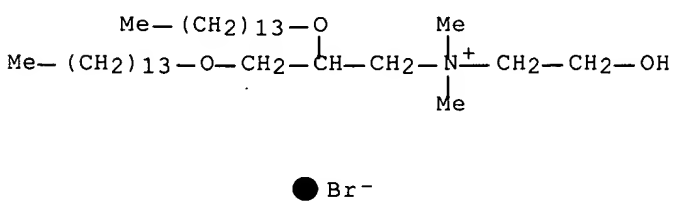
=> d ibib abs hitstr 12

L32 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:736678 HCAPLUS
DOCUMENT NUMBER: 130:91045
TITLE: Direct **gene** transfer to the respiratory tract of mice with pure plasmid and lipid-formulated **DNA**
AUTHOR(S): McCluskie, Michael J.; Chu, Yongliang; Xia, Jiu-Lin; Jessee, Joel; Gebyehu, Gulilat; Davis, Heather L.
CORPORATE SOURCE: Loeb Research Institute, Ottawa, Can.
SOURCE: Antisense Nucleic Acid Drug Dev. (1998), 8(5), 401-414
CODEN: ANADF5; ISSN: 1087-2906
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Direct **gene** transfer into the respiratory system could be carried out for either therapeutic or immunization purposes. Here we demonstrate that cells in the lung can take up and express plasmid **DNA** encoding a luciferase reporter **gene** whether it is administered in naked form or formulated with cationic liposomes. Depending on the lipid used, the transfection efficiency with liposome-formulated **DNA** may be higher, the same as, or less than that with pure plasmid **DNA**. Tetramethyltetraalkylspermine analogs with alkyl groups of 16 or 18 carbons and DMRIE/cholesterol formulations proved particularly effective. Similar results for reporter **gene** expression in the lung were obtained whether the **DNA** (naked or lipid formulated) was administered by indirect, non-invasive intranasal delivery (inhaled or instilled) or by invasive, direct intratracheal delivery (injected or via a cannula). Reporter **gene** expression peaks around 4 days, then falls off dramatically by 9 days. The dose-response is linear, at least up to 100 .mu.g plasmid **DNA**, suggesting better transfection efficiencies might be realized if there was not a vol. limitation. For a given dose of **DNA**, the best results are obtained when the **DNA** is mixed with the min. amt. of lipid that can complex it completely. These results are discussed in the context of direct **gene** transfer for either **gene** therapy or delivery of a mucosal **DNA vaccine**.

IT **153312-64-2**, DMRIE
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(direct **gene** transfer to respiratory tract of mice with pure plasmid and lipid-formulated **DNA**)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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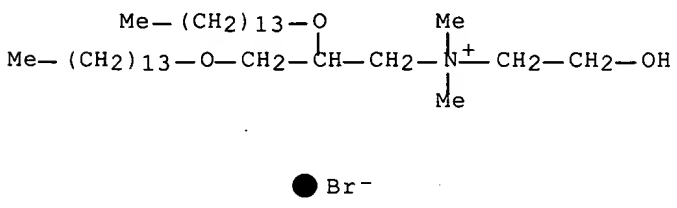
L32 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:249878 HCAPLUS
DOCUMENT NUMBER: 129:12373
TITLE: Transfection of primary tumor cells and tumor cell lines with plasmid **DNA**/lipid complexes
AUTHOR(S): Stopeck, Alison T.; Hersh, Evan M.; Brailey, Jacqueline L.; Clark, Paul R.; Norman, Jon; Parker, Suezanne E.
CORPORATE SOURCE: Arizona Cancer Center, Tucson, AZ, 85724-5024, USA
SOURCE: Cancer Gene Ther. (1998), 5(2), 119-126
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Appleton & Lange
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cancer **vaccines** that utilize genetically modified tumor cells require **gene** transfer methods capable of producing immunostimulatory doses of transgenes from fresh or short-term cultures of human tumor cells. Our studies optimize in vitro transfection of primary tumor cells using cationic lipids and a plasmid encoding the **gene** for human interleukin-2 (IL-2). Established tumor cell lines produced 10- to 100-fold more IL-2 than did fresh or short-term tumor cultures as measured by enzyme-linked immunoabsorbent anal. Importantly, transfection of primary tumor cells produced immunostimulatory levels of IL-2 as detd. by increased thymidine incorporation by autologous peripheral blood mononuclear cells and lymphokine-activated killer cell activity. IL-2 secretion by tumor cells persisted for at least 30 days post-transfection and was unaffected by freeze thawing or irradn. to 8000 rads. Multiple solid tumor types were successfully transfected, but normal blood mononuclear cells and leukemic blasts were resistant to transfection. Enzyme-linked immunoabsorbent anal. of the amt. of IL-2 secreted into the medium by transfected tumor cells correlated with the percentage of tumor cells expressing intracellular IL-2 as measured by flow cytometry. Plasmids utilizing a **cytomegalovirus** promoter yielded superior transfection efficiencies compared with plasmids contg. a Rous sarcoma **virus** promoter. These results suggest that a clin. **vaccine** trial using autologous tumor cells genetically modified to secrete IL-2 is feasible in patients with solid tumors.

IT **153312-64-2**, DMRIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(primary tumor cell and tumor cell line transfection with IL-2-encoding plasmid **DNA**/cationic lipid complexes)
RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 14

L32 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:473805 HCAPLUS
DOCUMENT NUMBER: 127:175118
TITLE: Development of improved vectors for **DNA** -based immunization and other **gene** therapy applications
AUTHOR(S): Norman, Jon A.; Hobart, Peter; Manthorpe, Marston; Felgner, Phil; Wheeler, Carl
CORPORATE SOURCE: Vical Inc., San Diego, CA, 92121, USA
SOURCE: Vaccine (1997), 15(8), 801-803
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Optimizing **gene** expression and delivery are necessary steps in the prodn. of vectors for **DNA**-based immunization as well as for other **gene** therapy applications. A mouse muscle/reporter **gene** assay system was used to systematically improve a plasmid **DNA** vector. The optimized vector VR1255 contained: (1) CMV promoter and enhancer; (2) CMV IE Intron A; (3) kanamycin resistance **gene**; (4) deleted SV40 origin of replication; (5) optimized lux coding region; and (6) a minimal synthetic terminator from the rabbit beta globin **gene**, mRBG. The vector VR1255 expressed 137 times greater than an earlier prototype RSV-based vector. For plasmid vector delivery into nonmuscle tissues, a recently synthesized cationic lipid, GAP-DLRIE, was found to greatly enhance the uptake and expression of plasmid **DNA** by 100-fold when instilled into the mouse lung. The time-course of CAT expression with GAP-DLRIE indicated that peak expression occurs 2-5 days after intranasal administration and expression diminished to about one-third the peak value by day 21. This cationic lipid may be useful for immunization by pulmonary and perhaps other nonmuscle routes.

IT **182919-20-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(development of improved vectors for **DNA**-based immunization and other **gene** therapy applications)

RN 182919-20-6 HCAPLUS
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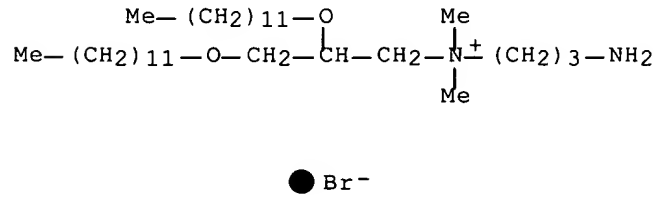

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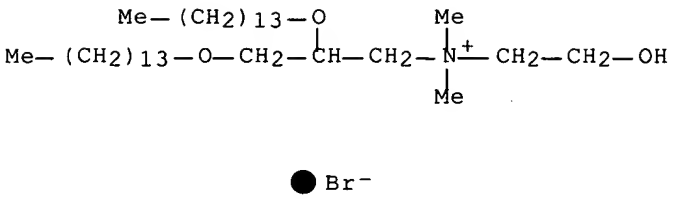
L39 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:280441 HCAPLUS
Correction of: 1997:206719
DOCUMENT NUMBER: 132:260257
Correction of: 126:301427
TITLE: Cationic liposome-mediated expression of HIV-regulated luciferase and diphtheria toxin A **genes** in HeLa cells infected with or expressing HIV
AUTHOR(S): Konopka, Krystyna; Harrison, Gail S.; Felgner, Philip L.; Duezguenes, Nejat
CORPORATE SOURCE: University of the Pacific, can Francisco, CA, 94115, USA
SOURCE: Biochim. Biophys. Acta (**1997**), 1356(2), 185-197
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB HIV-regulated expression of the diphtheria toxin A fragment **gene** (HIV-DT-A) is a potential **gene** therapy approach to AIDS. Since cationic liposomes are safe and non-**immunogenic** for in vivo **gene** delivery, the authors examd. whether LipofectAMINE or DMRIE reagent could mediate the transfection of HIV-DT-A (pTHA43) or the HIV-regulated luciferase **gene** (pLUCA43) into HIV-infected or uninfected HeLa cells. PLUCA43 was expressed at a 103-fold higher level in HeLa/LAV cells than in uninfected HeLa cells, while the extent of expression of RSV-regulated luciferase was the same in both cell lines. Co-transfection of HeLa cells with pTHA43 and the **proviral** HIV clone, HXB.DELTA.Bgl, resulted in complete inhibition of **virus** prodn. In contrast, the delivery of HIV-DT-A to chronically infected HeLa/LAV or HeLa/IIIB cells, or to HeLa CD4+ cells before infection, did not have a specific effect on **virus** prodn., since treatment of cells with control plasmids also reduced **virus** prodn. This redn. could be ascribed to cytotoxicity of the reagents. The efficiency of transfection, as measured by the percentage of cells expressing .beta.-gal, was .apprx.5. Thus, cationic liposome-mediated transfection was too inefficient to inhibit **virus** prodn. when the DT-A was delivered by cationic liposomes to chronically- or de novo-infected cells. However, when both the **virus** and DT-A **genes** were delivered into the same cells by cationic liposomes, DT-A was very effective at inhibiting **virus** prodn. The results indicate that the successful use of cationic liposomes for **gene** therapy will require the improvement of their transfection efficiency.
IT **153312-64-2**, DMRIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic liposome-mediated expression of HIV-regulated luciferase and diphtheria toxin A **genes** in HeLa cells infected with or expressing HIV in relation to **gene** therapy of AIDS)
RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



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L39 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:750931 HCAPLUS
DOCUMENT NUMBER: 130:109034
TITLE: **Immunotherapy** of established tumors in mice by intratumoral injection of interleukin-2 plasmid **DNA**: induction of CD8+ T-cell **immunity**
AUTHOR(S): Saffran, Douglas C.; Horton, Holly M.; Yankauckas, Michelle A.; Anderson, Deborah; Barnhart, Kerry M.; Abai, Anna M.; Hobart, Peter; Manthorpe, Marston; Norman, Jon A.; Parker, Suezanne E.
CORPORATE SOURCE: Vical Inc., San Diego, CA, 92121, USA
SOURCE: Cancer Gene Ther. (**1998**), 5(5), 321-330
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

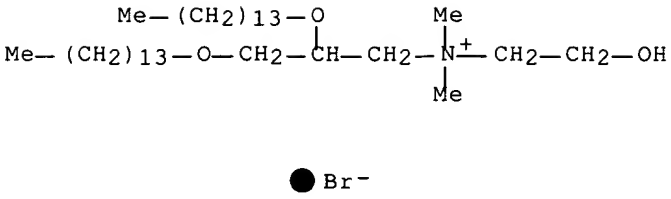
AB Intratumoral (i.t.) injection of a plasmid **DNA** vector encoding the murine interleukin-2 (IL-2) **gene** was used to treat established renal cell carcinoma (Renca) tumors in BALB/c mice. Tumor regression was obsd. in 60-90% of mice that were injected i.t. for 4 days with IL-2 plasmid **DNA** complexed with the cationic lipid DMRIE/DOPE ((.+-.)-N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide/dioleoylphosphatidylethanolamine). The mice remained tumor-free until the conclusion of the study, which was 4 mo after tumor challenge. In a rechallenge expt., mice that were rendered tumor-free for 6 mo by IL-2 plasmid **DNA** treatment rejected a subsequent challenge of Renca cells but could not reject a challenge with the unrelated, syngeneic CT-26 tumor. Spleen cells from cured mice contained Renca-specific cytotoxic T lymphocytes, and adoptive transfer of mixed lymphocyte cultures into naive mice at 2 days after challenge with Renca cells prevented tumor growth. In vivo depletion of T-cell subsets at the time of i.t. injection with IL-2 plasmid **DNA** demonstrated that CD8+ T cells, but not CD4+ T cells, were the primary effectors of the antitumor response.

IT **213186-72-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**immunotherapy** of established tumors in mice by intratumoral injection of interleukin-2 plasmid **DNA** induces CD8+ T-cell **immunity**)

RN 213186-72-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide, mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 153312-64-2
CMF C35 H74 N O3 . Br

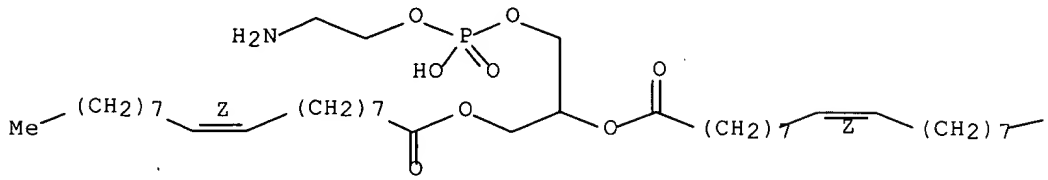


CM 2

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 3

L39 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:750929 HCAPLUS
DOCUMENT NUMBER: 130:108901
TITLE: Lipofection indirectly increases expression of endogenous major histocompatibility complex class I molecules on tumor cells
AUTHOR(S): Fox, Bernard A.; Drury, Marcie; Hu, Hong-Ming; Cao, Zhuwei; Huntzicker, Erik G.; Qie, Wenxia; Urba, Walter J.
CORPORATE SOURCE: Laboratory of Molecular and Tumor Immunology, Robert W. Franz Cancer Research Center, Providence Portland Medical Center, Earle A. Chiles Research Institute, Portland, OR, 97213, USA
SOURCE: Cancer Gene Ther. (**1998**), 5(5), 307-312
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

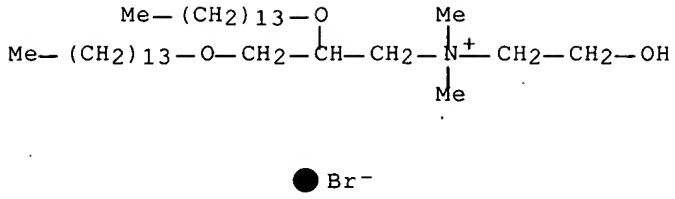
AB Direct intratumoral injection of a lipid/**DNA** complex encoding an allogeneic major histocompatibility complex (MHC) class I mol. leads to regression of both an **immunogenic** murine tumor and also melanoma lesions in some patients. We have sought to understand the mechanism(s) for this augmentation of antitumor activity. While optimizing parameters for in vitro **gene** transfer into the D5 subclone of B16BL6, it was noted that lipofected tumors not only expressed the new alloantigen but also exhibited increased expression of endogenous MHC class I, both H-2 Kb and H-2 Db. This increase in expression was not restricted to the small percentage of cells that expressed the transfected **gene**, but appeared to affect the majority of cells in culture. Class I expression was not increased by lipopolysaccharide, **DNA** alone, lipid, or lipid/lipopolysaccharide mixts. Enhanced class I expression required a **DNA**/lipid complex and was greatest when parameters optimized for **gene** transfer of the alloantigen were used. All **DNA** plasmids tested had this effect, including one plasmid whose **DNA** was not transcribed because it lacked an expression cassette. Because of the crit. role that MHC class I antigens play in **immune** recognition, we propose that lipid complex-mediated **gene** transfer may provide **immunol**. advantages beyond those that are attributable to expression of the specific **gene** transferred.

IT **213186-72-2**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipofection indirectly increases expression of endogenous MHC class I mols. on tumor cells and enhances antitumor activity)

RN 213186-72-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide, mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 153312-64-2
CMF C35 H74 N O3 . Br

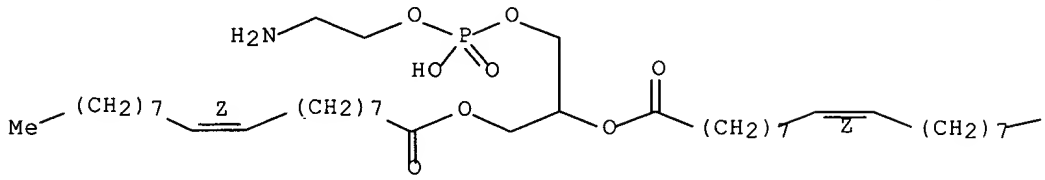


CM 2

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 4

L39 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:517159 HCAPLUS
DOCUMENT NUMBER: 129:188218
TITLE: Lipid-mediated **gene** transfer of **viral** IL-10 prolongs vascularized cardiac allograft survival by inhibiting donor-specific cellular and humoral **immune** responses
AUTHOR(S): DeBruyne, L. A.; Li, K.; Chan, S. Y.; Qin, L.; Bishop, D. K.; Bromberg, J. S.
CORPORATE SOURCE: Dep. Surg., Univ. Michigan Med. Cent., Ann Arbor, MI, 48109, USA
SOURCE: Gene Ther. (**1998**), 5(8), 1079-1087
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **gene** encoding the **immunosuppressive** cytokine **viral** interleukin-10 (vIL-10) was introduced into BALB/c (H-2d) vascularized cardiac allografts by perfusing the graft vasculature with **DNA**-liposome complexes, utilizing the exptl. cationic lipid .gamma.AP DLRIE/DOPE and a plasmid encoding vIL-10 under the control of the HCMVie promoter. The **DNA** to lipid ratio and **DNA** dose were crit. factors in obtaining optimal biol. effects. **Gene** transfer of vIL-10 with a 3:1 **DNA** to lipid wt. ratio using 375 .mu.g **DNA** significantly prolonged allograft survival in MHC-mis-matched C57BL/6 (H-2b) recipients (16.00 days) compared with both unmodified allografts (8.14 days) and vIL-10 anti-sense controls (8.28 days). Enhanced graft survival was specific to vIL-10 expression since treatment with anti-sense plasmid or anti-vIL-10 monoclonal antibody (mAb) abrogated the effect. Prolonged survival was assocd. with a novel histol. characterized by a moderate mono-nuclear infiltrate, edema, and diffuse fibrillar/collagen deposition in the interstitium. Despite these morphol. changes, myocytes remained viable and vessels were patent. Limiting diln. anal. revealed transient infiltration of IL-2 secreting, donor-reactive, helper T lymphocytes (HTL) and cytotoxic T lymphocytes (CTL) in vIL-10 expressing grafts on day 7, the decreased significantly by day 14. Similarly, vIL-10 **gene** transfer inhibited the accumulation of donor-specific HTL and CTL in the spleen, compared with antisense controls. Prolonged survival was also assocd. with a marked decrease in IgM and IgG alloantibody prodn., with little to no IgG isotype switching. These results show that **viral** IL-10 **gene** transfer inhibits graft rejection in a clin. relevant model by inhibiting donor-specific cellular and humoral **immune** responses.

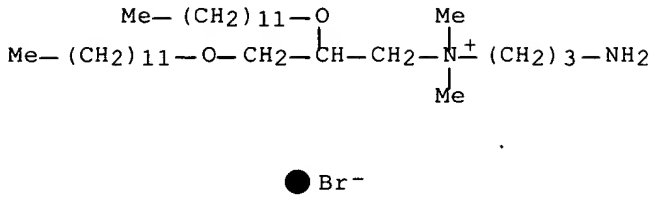
IT **200357-85-3**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipid-mediated **gene** transfer of **viral** IL-10 prolongs vascularized cardiac allograft survival)

RN 200357-85-3 HCAPLUS
CN 1-Propanaminium, N-(3-aminopropyl)-2,3-bis(dodecyloxy)-N,N-dimethyl-, bromide, mixt. with 1-[[[(2-aminoethoxy)hydroxyphosphinyl]oxy]methyl]-1,2-ethanediyl di-(9Z)-9-octadecenoate (9CI) (CA INDEX NAME)

CM 1

CRN 182919-20-6

CMF C32 H69 N2 O2 . Br

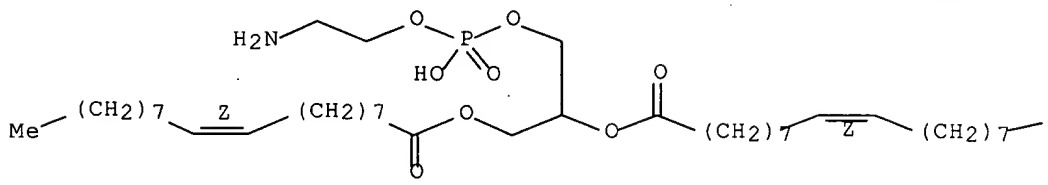


CM 2

CRN 2462-63-7
CMF C41 H78 N O8 P
CDES *

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

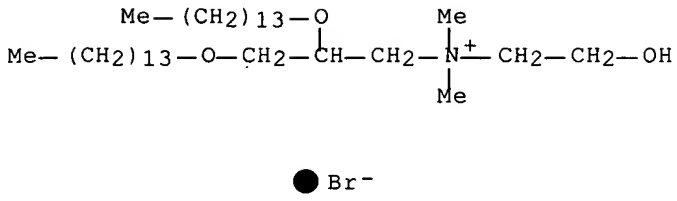
=> d ibib abs hitstr 5

L39 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:300574 HCAPLUS
DOCUMENT NUMBER: 127:32672
TITLE: Phase I study of **immunotherapy** of hepatic metastases of colorectal carcinoma by direct **gene** transfer of an allogeneic histocompatibility antigen, HLA-B7
AUTHOR(S): Rubin, J.; Galanis, E.; Pitot, H. C.; Richardson, R. L.; Burch, P. A.; Charboneau, J. W.; Reading, C. C.; Lewis, B. D.; Stahl, S.; Akporiaye, E. T.; Harris, D. T.
CORPORATE SOURCE: Div. Med. Oncology, Mayo Clinic and Mayo Foundation, Rochester, MN, USA
SOURCE: Gene Ther. (**1997**), 4(5), 419-425
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have completed a phase I study to test feasibility and toxicity of **immunotherapy** of hepatic metastases from colorectal carcinoma by direct **gene** transfer of HLA-B7, a MHC class I **gene**. Eligible patients were HLA-B7 neg., **immunocompetent** by PHA lymphocyte stimulation and had at least two measurable hepatic lesions on CT scan for measurement of response of the injected lesion, as well as evaluation of possible distant response. Under ultrasonog. guidance the hepatic lesions were injected with Allovectin-7, a liposomal vector contg. the combination of the HLA-B7 **gene** with .beta.2-microglobulin formulated with the lipid DMRIE-DOPE. Eligible patients were injected on two schedules. On the first schedule patients received an injection on day 1 and the injected lesion was biopsied to det. transfection every 2 wk for 8 wk. Doses were escalated from 10 .mu.g to 50 .mu.g to 250 .mu.g with three patients treated at each level. The second schedule included multiple injections of 10 .mu.g. Three patients received injection on days 1 and 15. Three patients received injections on days 1, 15 and 29. A total of 15 patients have completed treatment. The plasmid **DNA** was detected in 14 of 15 patients (93%) by PCR. In five of 15 patients (33%) mRNA was also detected. The HLA-B7 protein was detected in five of eight patients (63%) by **immunohistochem.** and in seven of 14 patients (50%) tested by fluorescence activated cell sorting (FACS) anal. There has been no serious toxicity directly attributable to Allovectin-7. The results suggest that liposomal **gene** transfer by direct injection is feasible and non-toxic. Further studies will be necessary to establish the therapeutic efficacy.

IT **153312-64-2**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**gene** transfer of allogeneic HLA-B7 to human hepatic metastases of colorectal carcinoma)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)

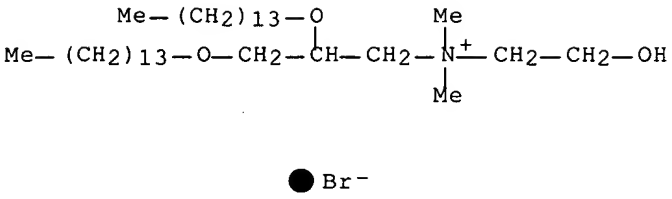


=> d ibib abs hitstr 6

L39 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:206719 HCAPLUS
DOCUMENT NUMBER: 126:301427
TITLE: Cationic liposome-mediated expression of HIV-regulated luciferase and diphtheria toxin A **genes** in HeLa cells infected with or expressing HIV
AUTHOR(S): Konopka, Krystyna; Harrison, Gail S.; Felgner, Philip L.; Nejat Duezguenes
CORPORATE SOURCE: Department of Microbiology, School of Dentistry, University of the Pacific, 2155 Webster Street, San Francisco, CA, 94115, USA
SOURCE: Biochim. Biophys. Acta (**1997**), 1356(2), 185-197
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HIV-regulated expression of the diphtheria toxin A fragment **gene** (HIV-DT-A) is a potential **gene** therapy approach to AIDS. Since cationic liposomes are safe and non-**immunogenic** for in vivo **gene** delivery, the authors examd. whether LipofectAMINE or DMRIE reagent could mediate the transfection of HIV-DT-A (pTHA43) or the HIV-regulated luciferase **gene** (pLUCA43) into HIV-infected or uninfected HeLa cells. PLUCA43 was expressed at a 103-fold higher level in HeLa/LAV cells than in uninfected HeLa cells, while the extent of expression of RSV-regulated luciferase was the same in both cell lines. Co-transfection of HeLa cells with pTHA43 and the **proviral** HIV clone, HXB.DELTA.Bgl, resulted in complete inhibition of **virus** prodn. In contrast, the delivery of HIV-DT-A to chronically infected HeLa/LAV or HeLa/IIIB cells, or to HeLa CD4+ cells before infection, did not have a specific effect on **virus** prodn., since treatment of cells with control plasmids also reduced **virus** prodn. This redn. could be ascribed to cytotoxicity of the reagents. The efficiency of transfection, as measured by the percentage of cells expressing .beta.-gal, was .apprx.5. Thus, cationic liposome-mediated transfection was too inefficient to inhibit **virus** prodn. when the DT-A was delivered by cationic liposomes to chronically- or de novo-infected cells. However, when both the **virus** and DT-A **genes** were delivered into the same cells by cationic liposomes, DT-A was very effective at inhibiting **virus** prodn. The results indicate that the successful use of cationic liposomes for **gene** therapy will require the improvement of their transfection efficiency.

IT **153312-64-2**, DMRIE
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic liposome-mediated expression of HIV-regulated luciferase and diphtheria toxin A **genes** in HeLa cells infected with or expressing HIV in relation to **gene** therapy of AIDS)
RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



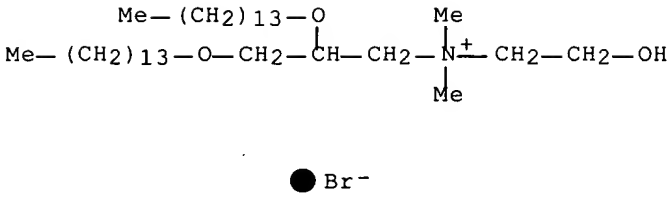
=> d ibib abs hitstr 7

L39 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:7136 HCAPLUS
DOCUMENT NUMBER: 126:98777
TITLE: Efficiency of plasmid delivery and expression after lipid-mediated **gene** transfer to human cells in vitro
AUTHOR(S): Bebok, Zsuzsa; Abai, Anna M.; Dong, Jian-Yun; King, Scott A.; Kirk, Kevin L.; Berta, Gabor; Hughes, Brian W.; Kraft, Andrew S.; Burgess, Stephen W.; Shaw, Walter; Felgner, Philip L.; Sorscher, Eric J.
CORPORATE SOURCE: Gregory Fleming James Cystic Fibrosis Research Center, Univ. of Alabama at Birmingham, Birmingham, AL, USA
SOURCE: J. Pharmacol. Exp. Ther. (**1996**), 279(3), 1462-1469
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cationic liposome-mediated **gene** transfer has become increasingly important in the development of exptl. therapies for human diseases, such as melanoma, human **immunodeficiency virus** infection, cystic fibrosis and alpha-1 antitrypsin deficiency. However, very little is known about the mechanisms by which lipid-mediated **gene** transfer occurs. We studied the kinetics of plasmid delivery and expression by using this technique. Plasmid entry in the cystic fibrosis respiratory epithelial cell line 2CFSME0-, as well as in two other cell lines (HeP 2g and HeLa) occurred in 95 to 100% of cells within 1 h of the initiation of lipid-mediated **gene** transfer. In hepatic and respiratory cells, transcription of a construct contg. the cystic fibrosis transmembrane conductance regulator was obsd. in more than 80% of the cell population; similarly high levels of plasmid utilization were obtained in studies of HLA-B7 expression in human melanoma cells. Studies directly relevant to current human trials of lipid-mediated **gene** transfer indicate that plasmid entry, transcription and translation are often surprisingly efficient, and may occur in nearly 100% of human cells in culture when sensitive methods for detection are used. Furthermore, conventional X-gal **immunohistochem**. markedly underestimates transfection efficiency during transient **gene** expression. These studies point to a new mechanistic understanding of the features that limit expression by using cationic liposomes.

IT **153312-64-2**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(efficiency of plasmid delivery and expression after lipid-mediated **gene** transfer to human cells in vitro)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



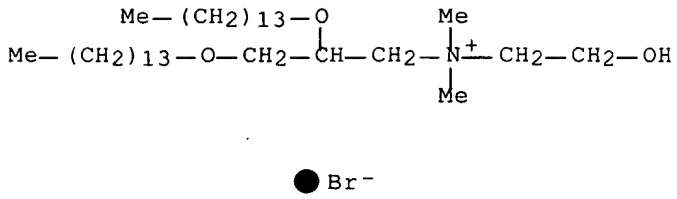
=> d ibib abs hitstr 8

L39 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:394944 HCAPLUS
DOCUMENT NUMBER: 125:140291
TITLE: Human **immunodeficiency virus** type-1 (HIV-1) infection increases the sensitivity of macrophages and THP-1 cells to cytotoxicity by cationic liposomes
AUTHOR(S): Konopka, Krystyna; Pretzer, Elizabeth; Felgner, Philip L.; Duezguenes, Nejat
CORPORATE SOURCE: Department of Microbiology, University of the Pacific School of Dentistry, 2155 Webster Street, San Francisco, CA, 94115, USA
SOURCE: Biochim. Biophys. Acta (**1996**), 1312(3), 186-196
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cationic liposomes may be valuable for the delivery of anti-sense oligonucleotides, ribozymes, and therapeutic **genes** into human **immunodeficiency virus** type 1 (HIV-1)-infected and uninfected cells. We evaluated the toxicity of three cationic liposomal prepns., Lipofectamine, Lipofectin, and 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DMRIE) reagent, to HIV-infected and uninfected cells. Monocyte/macrophages were infected with HIV-1BaL and treated with liposomes in medium contg. 20 fetal bovine serum (FBS) for 4 h or 24 h at 37.degree.C. Uninfected monocytic THP-1 cells and chronically infected THP-1/HIV-1IIIB cells were treated with phorbol 12-myristate 13-acetate (PMA) and exposed to liposomes in the presence of 10 FBS. Toxicity was evaluated by the Alamar Blue assay and **viral** p24 prodn. The toxic effect of cationic liposomes was very limited with uninfected cells, although concns. of liposomes that were not toxic within a few days of treatment could cause toxicity at later times. In HIV-1BaL-infected macrophages, Lipofectamine (up to 8 .mu.M) and Lipofectin (up to 40 .mu.M) were not toxic after a 4-h treatment, while DMRIE reagent at 40 .mu.M was toxic. While a 4-h treatment of THP-1/HIV-1IIIB cells with the cationic liposomes was not toxic, even up to 14 days post-treatment, all three cationic liposomes were toxic to cells at the highest concn. tested after a 24-h treatment. Similar results were obtained with the Alamar Blue assay, Trypan Blue exclusion and a method that enumerates nuclei. Infected cells with relatively high overall viability could be impaired in their ability to produce virions, indicating that **virus** prodn. appears to be more sensitive to treatment with the cationic liposomes than cell viability. Our results indicate that HIV-infected cells are more susceptible than uninfected cells to killing by cationic liposomes. The mol. basis of this differential effect is unknown; it is proposed that alterations in cellular membranes during **virus** budding cause enhanced interactions between cationic liposomes and cellular membranes.

IT **153312-64-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(HIV-1 **virus** infection increases the sensitivity of macrophages and THP-1 cells to cytotoxicity by cationic liposomes)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



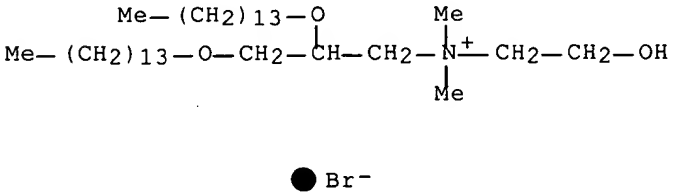
=> d ibib abs hitstr 9

L39 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:645758 HCAPLUS
DOCUMENT NUMBER: 123:102145
TITLE: Cancer **gene** therapy using plasmid **DNA**: safety evaluation in rodents and non-human primates
AUTHOR(S): Parker, Suezanne E.; Vahlsing, H. Lee; Serfilippi, Laurie M.; Franklin, Craig L.; Doh, Soeun G.; Gromkowski, Stanislaw H.; Lew, Denise; Manthorpe, Marston; Norman, Jon
CORPORATE SOURCE: Vical Inc., San Diego, CA, 92121, USA
SOURCE: Hum. Gene Ther. (**1995**), 6(5), 575-90
CODEN: HGTHE3; ISSN: 1043-0342
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate the safety of a plasmid **DNA**-lipid complex, a series of good lab. practice (GLP) safety studies were conducted with VCL-1005, a plasmid **DNA** expression vector contg. both the human class I MHC HLA-B7 heavy-chain and the .beta.2-microglobulin (.beta.2m) light-chain **genes** formulated with the cationic lipid, DMRIE/DOPE. In mice, the repeated i.v. injection of VCL-1005 at plasmid **DNA** doses of 0.1, 1.0, or 10 .mu.g for 14 days had only incidental effects on clin. chem. and hematol., and did not result in any organ pathol. Repeated intrahepatic injections of VCL-1005 in mice did not result in significant liver histopathol. or significant alterations in liver enzymes. In cynomolgus monkeys, the repeated i.v. administration of VCL-1005 at a cumulative dose of 720 .mu.g of **DNA** had no effects on clin. chem., hematol., or organ pathol. Thus, systemic administration of a plasmid **DNA** expression vector contg. the coding sequence for a foreign MHC class I mol. did not result in significant toxicity or a pathol. **immune** response in animals. These results suggest that the direct transfer of VCL-1005, a plasmid **DNA**-lipid complex, could be used for the safe in vivo delivery of recombinant **DNA** for a cancer **gene** therapy trial.

IT **153312-64-2D**, complexes with plasmid **DNA**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety evaluation in rodents and non-human primates for cancer **gene** therapy using plregasmid **DNA**-lipid complex)

RN 153312-64-2 HCAPLUS
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 1

L50 ANSWER 1 OF 9 USPATFULL
ACCESSION NUMBER: 2002:32536 USPATFULL
TITLE: Compositions and methods for in vivo delivery of polynucleotide-based therapeutics
INVENTOR(S): Manthorpe, Marston, San Diego, CA, UNITED STATES
Hartikka, Jukka, San Diego, CA, UNITED STATES
Sukhu, Loretta, San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): Vical Incorporated, San Diego, CA (U.S. corporation)

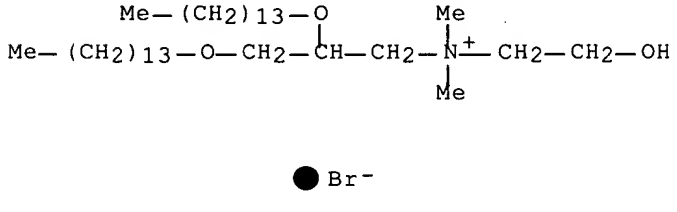
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002019358	A1	20020214
APPLICATION INFO.:	US 2001-839574	A1	20010423 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-198823	20000421 (60)
	US 2000-253153	20001128 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STERNE, KESSLER, GOLDSTEIN & FOX PLLC, 1100 NEW YORK AVENUE, N.W., SUITE 600, WASHINGTON, DC, 20005-3934
NUMBER OF CLAIMS: 163
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 29 Drawing Page(s)
LINE COUNT: 4605
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

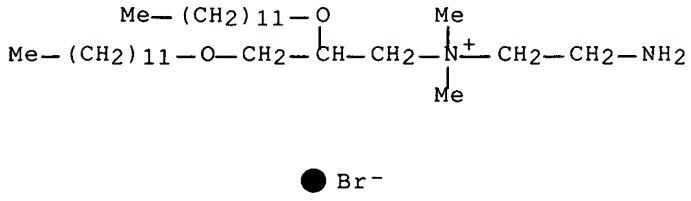
AB The present invention relates to pharmaceutical compositions and methods to improve expression of exogenous polypeptides into vertebrate cells in vivo, utilizing delivery of polynucleotides encoding such polypeptides. More particularly, the present invention provides the use of salts, in particular sodium and potassium salts of phosphate, in aqueous solution, and auxiliary agents, in particular detergents and surfactants, in pharmaceutical compositions and methods useful for direct polynucleotide-based polypeptide delivery into the cells of vertebrates.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153312-64-2**, Dmrie **208040-06-6**, Gap dlrie
299207-54-8, Gap-dmorie
(compns. and methods for in vivo delivery of polynucleotide-based therapeutics)
RN 153312-64-2 USPATFULL
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



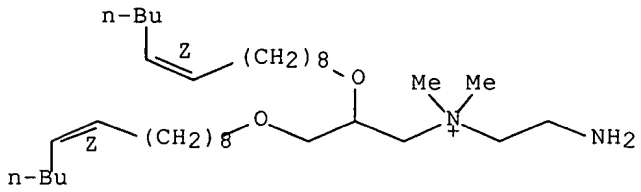
RN 208040-06-6 USPATFULL
CN 1-Propanaminium, N-(2-aminoethyl)-2,3-bis(dodecyloxy)-N,N-dimethyl-,

bromide (9CI) (CA INDEX NAME)

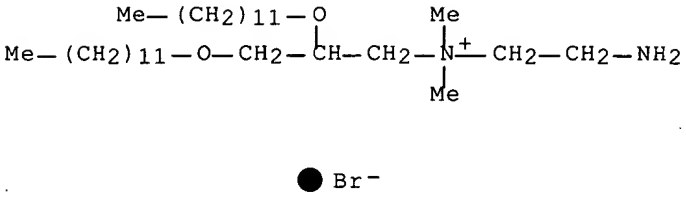


RN 299207-54-8 USPATFULL
CN 1-Propanaminium, N-(2-aminoethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.

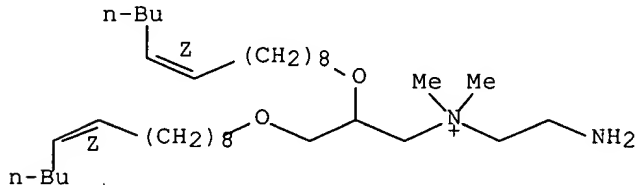


bromide (9CI) (CA INDEX NAME)



RN 299207-54-8 USPATFULL
CN 1-Propanaminium, N-(2-aminoethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-tetradecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



=> d ibib abs hitstr 2

L50 ANSWER 2 OF 9 USPATFULL

ACCESSION NUMBER:	2002:9855 USPATFULL
TITLE:	Peptide-lipid conjugates, liposomes and lipsomal drug delivery
INVENTOR(S):	Meers, Paul R., Princeton, NJ, United States Pak, Charles, Princeton, NJ, United States Ali, Shaukat, Monmouth Junction, NJ, United States Janoff, Andrew, Yardley, PA, United States Franklin, J. Craig, Skillman, NJ, United States Erukulla, Ravi K., Plainsboro, NJ, United States Cabral-Lilly, Donna, Princeton, NJ, United States Ahl, Patrick L., Princeton, NJ, United States
PATENT ASSIGNEE(S):	Elan PharmaceuticalsTechnologies, Inc., King of Prussia, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6339069	B1	20020115
APPLICATION INFO.:	US 1999-343650		19990629 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-168010, filed on 7 Oct 1998, now patented, Pat. No. US 6143716 Division of Ser. No. US 1997-950618, filed on 15 Oct 1997, now patented, Pat. No. US 6087325

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-27544	19961015 (60)
	US 1997-39183	19970227 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Nguyen, Dave T.
LEGAL REPRESENTATIVE:	Burns, Doane, Swecker & Mathis L.L.P.
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	38 Drawing Figure(s); 27 Drawing Page(s)
LINE COUNT:	2321

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

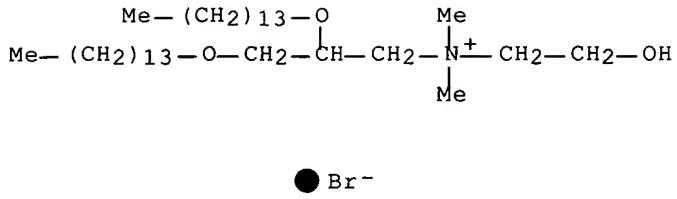
AB Peptide-lipid conjugates are incorporated into liposomes so as to selectively destabilize the liposomes in the vicinity of target peptidase-secreting cells, and hence, to deliver the liposomes to the vicinity of the target cells, or directly into the cells. The liposomes can thus be used to treat mammals for diseases, disorders or conditions, e.g., tumors, microbial infection and inflammations, characterized by the occurrence of peptidase-secreting cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **153312-64-2**, Dmrie
(peptide-lipid conjugates, liposomes and liposomal drug delivery to peptidase-secreting cells)

RN 153312-64-2 USPATFULL

CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d kwic 2

L50 ANSWER 2 OF 9 USPATFULL

DETD . . . tissue plasminogen activator and urokinase, stromelysin, human collagenases, cathepsins, lysozyme, granzymes, dipeptidyl peptidases, peptide hormone-inactivating enzymes, kininases, bacterial peptidases and **viral** proteases. Elastase, for example, is involved in tumor cell tissue remodeling; the breast cancer cell line MCF-7 has been shown. . .

DETD . . . or diagnostic, activity in animals. Bioactive agents which may be associated with the liposomes include, but are not limited to: **antiviral** agents such as acyclovir, zidovudine and the interferons; antibacterial agents such as aminoglycosides, cephalosporins and tetracyclines; antifungal agents such as. . .

DETD . . . Dipeptidylaminopeptidase IV (DAP IV, EC 3.4.14.5), a member of the dipeptidyl peptidase enzyme family, is found in increased concentrations on **pig** aorta smooth muscle cells (Palmieri et al., 1989). Vessel wall damage, e.g., after angioplasty or during other inflammatory states exposes. . .

CLM What is claimed is:

. . . elastase, plasmin, plasminogen activator, urokinase; stromelysin, human collagenases, cathepsins, lysozyme, granzymes, dipeptidyl peptidases, peptide hormone-inactivating enzymes, kininases, bacterial peptidases and **viral** proteases.

22. The method of claim 1, wherein the bioactive agent is selected from the group consisting of **antiviral** agents, antibacterial agents, antifungal agents, antineoplastic agents, antiinflammatory agents, radiolabels, radiopaque compounds, fluorescent compounds, mydriatic compounds, bronchodilators, local anesthetics, nucleic. . .

IT 623-57-4D, diacyl derivs. 2462-63-7, Dope 5681-36-7, Dipalmitoyl phosphatidylethanolamine 10015-88-0, Pope 127512-29-2, DODAP 137056-72-5, Dc-chol 144189-73-1, Dotap **153312-64-2**, Dmrie 159910-11-9 165467-64-1, Dori 171730-61-3 389063-75-6
(peptide-lipid conjugates, liposomes and liposomal drug delivery to peptidase-secreting cells)

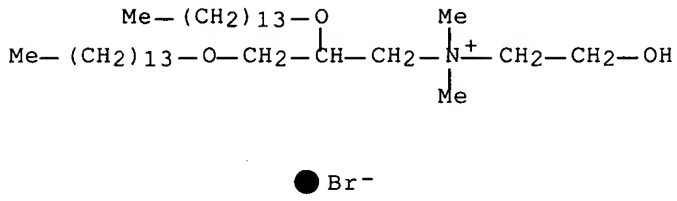
=> d ibib abs hitstr 3

L50 ANSWER 3 OF 9 USPATFULL
ACCESSION NUMBER: 2001:179076 USPATFULL
TITLE: Compositions and methods for nucleic acid delivery to the lung
INVENTOR(S): Eljamal, Mohammed, San Jose, CA, United States
Patton, John S., San Carlos, CA, United States
Foster, Linda, Sunnyvale, CA, United States
Platz, Robert M., Half Moon Bay, CA, United States
PATENT ASSIGNEE(S): Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6303582	B1	20011016
APPLICATION INFO.:	US 1999-427836		19991026 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-422563, filed on 14 Apr 1995, now patented, Pat. No. US 5994314 Continuation-in-part of Ser. No. US 1995-417507, filed on 4 Apr 1995, now abandoned Continuation of Ser. No. US 1993-44358, filed on 7 Apr 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: LeGuyader, John L.
ASSISTANT EXAMINER: Larson, Thomas G
LEGAL REPRESENTATIVE: Evans, Susan T., Cagan, Felissa H., Hurst, Stephen L.
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 853
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A dry powder composition comprises nucleic acid constructs dispersed within with a hydrophilic excipient material, where the powder particles have an average size in the range from 0.5 .mu.m to 50 .mu.m. Nucleic acid constructs may comprise bare nucleic acid molecules, **viral** vectors, or vesicle structures. The hydrophilic excipient material will be selected to stabilize the nucleic acid molecules in the constructs, enhance dispersion of the nucleic acid in dry powder aerosols, and enhance wetting of the nucleic acid constructs as they are delivered to moist target locations within the body.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153312-64-2D**, complexes with DNA
(compns. and methods for nucleic acid delivery to lungs in gene therapy)
RN 153312-64-2 USPATFULL
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d kwic 3

L50 ANSWER 3 OF 9 USPATFULL

AB . . . average size in the range from 0.5 .mu.m to 50 .mu.m. Nucleic acid constructs may comprise bare nucleic acid molecules, **viral** vectors, or vesicle structures. The hydrophilic excipient material will be selected to stabilize the nucleic acid molecules in the constructs,. . .

SUMM . . . distribution, but requires time-consuming equipment set-up, can require prolonged periods of treatment to achieve an adequate dosage, can inactivate a **viral** carrier, and can result in undesirable aggregation or degradation of the nucleic acids within the aerosol mist. Aggregated nucleic acids. . .

SUMM . . . of an .alpha.1-antitrypsin gene to rats, with secretion of the gene product being observable for at least one week. An **adenoviral** vector containing the gene was diluted in saline and instilled directly into the rat trachea. Underwood et al. (1991) J. PHARMACOL. METH. 26:203-210, describes the administration of dry powder bronchodilators in a lactose carrier to **pig** lungs. U.S. Pat. No. 5,049,388 describes the delivery of liquid aerosols containing liposomes to the lungs. Friedman (1989) SCIENCE 244:1275-1281. . .

SUMM . . . sizes being useful for delivery to other moist target locations. The nucleic acid constructs may comprise bare nucleic acid molecules, **viral** vectors, associated **viral** particle vectors, nucleic acids present in a vesicle, or the like.

SUMM . . . by drying the same liposome vesicles in buffered solutions. In contrast, aqueous solutions in which the nucleic acid constructs comprise **viral** vectors usually will be buffered to enhance stability of the **viral** vectors.

DETD A first type of such delivery vehicles comprises **viral** vectors, such as retroviruses, adenoviruses, and adeno-associated viruses, which have been inactivated to prevent self-replication but which maintain the native **viral** ability to bind a target host cell, deliver genetic material into the cytoplasm of the target host cell, and promote expression of structural or other genes which have been incorporated in the particle. Suitable **retrovirus** vectors for mediated gene transfer are described in Kahn et al. (1992) CIRC. RES. 71:1508-1517, the disclosure of which is incorporated herein by reference. A suitable **adenovirus** gene delivery system is described in Rosenfeld et al. (1991) SCIENCE 252:431-434, the disclosure of which is incorporated herein by reference. Both **retroviral** and **adenovirus** delivery systems are described in Friedman (1989) SCIENCE 244:1275-1281, the disclosure of which is also incorporated herein by reference.

DETD It is also possible to combine these two types of delivery systems, i.e., lipids and **viral** vectors. For example, Kahn et al. (1992), supra., teaches that a **retrovirus** vector may be combined in a cationic DEAE-dextran vesicle to further enhance

transformation efficiency. It is also possible to incorporate nuclear proteins into **viral** and/or liposomal delivery vesicles to even further improve transfection efficiencies. See, Kaneda et al. (1989) SCIENCE 243:375-378, the disclosure of. . .

DETD In the case of nucleic acid constructs comprising **viral** vectors, it is usually desirable that the aqueous solution be buffered in order to enhance the activity of the **viral** vectors after drying.

DETD 1. pCMV.beta. (Genzyme, Framingham, Mass.). pCMV-.beta.-gal: **Cytomegalovirus** promoter was linked to the Escherichia coli Lac-Z gene, which codes for the enzyme .beta.-galactosidase. The activity of this enzyme. . .

DETD 2. pCIS-CAT (Megabios, San Francisco, Calif.). pCIS-CAT: Chloramphenicol acetyltransferase (CAT) fused to the human **cytomegalovirus** (CMV) immediate early promoter/enhancer element.

DETD **Virus**

DETD Ad2-CMV-LacZ-2 (Genzyme, Framingham, Mass.). AD2-CMV-Lac-Z: **Cytomegalovirus** promoter was linked to the Escherichia coli Lac-Z gene and was incorporated into replication deficient recombinant **virus**. Takiff et al. (1984) J. VIROL. 51:131-136 and Gilardi et al. (1990) FEBS LETT. 267:60-62.

DETD **Adenovirus** (40.20 mg/ml)

DETD . . . 305.3 mg sucrose (Sigma, Lot No. 69F0026), 77.9 mg NaCl (VWR SCI., Lot No. 34005404) and 0.1 ml of Ad2-CMV-LacZ **virus** (10.sup.11 iu/ml with particle concentration of .about.5.times.10.sup.12 /ml in PBS+3% sucrose, Genzyme) in 10 ml phosphate buffer. This solution was. . .

DETD Spray Dried Powder Preparation: **Adenoviral** Vector (CFTR Gene)/Mannitol Formulation

DETD . . . a particle diameter from 1 .mu.m to 5 .mu.m is formed as follows. The CFTR gene is linked to the **adenovirus** (Ad) late promoter, and the resulting expression cassette is incorporated into an **adenovirus** vector, as taught in Rosenfeld et al. (1991) SCIENCE 252:431-434. The **adenovirus** vector has a deletion in the E3 region, thus permitting encapsidation of the recombinant genomic DNA including the CFTR gene. The vector further has a deletion in the Elq region, preventing **viral** replication.

DETD Sufficient **adenovirus** vector is added to a phosphate buffered saline solution (0.15 mM NaCl, 2.7 mM KCl, 8.1 mM Na.sub.2 PO.sub.4, 1.5. . .

DETD . . . CLONING: A LABORATORY MANUAL, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. The .alpha.1AT gene is fused to the human **cytomegalovirus** (CMV) immediate early promoter/enhancer element. The plasmid is then purified by alkaline lysis and ammonium acetate precipitation, and the nucleic. . .

DETD Transfection of Cells with Lipid:DNA Complexes and **Adenovirus** Vectors

DETD . . . processed and unprocessed DNA in the gel electrophoresis. As expected, the reconstituted DNA (without any delivery vehicle, cationic lipid or **adenovirus**) powder did not show any transfection activity in the in-vitro cytofection assay.

DETD **Adenovirus** Vector Constructs Useful for Gene Therapy: Dry Powder Aerosols

DETD . . . the effects of bulking agents in phosphate buffer (PB), (i) mannitol/HSA, (ii) glycine/HSA and (iii) mannitol/glycine/HSA, on the infectivity of **adenovirus** dry powders were investigated. In the second set, the effects of buffer removal and process outlet temperature on **viral** infectivity were investigated. All solutions were used and stored cold (about 5.degree. C.).

DETD . . . mannitol/HSA in PB formulations were prepared as follows. To

four samples of 4.times.3 ml mannitol/HSA was added 0.1 ml of **adenovirus** solution to obtain 3.2.times.10.sup.7 iu/ml and about 60 mg/ml solids. The fifth mannitol/HSA solution was used as a control with no **virus**. Two of the **virus**-containing samples were diluted with de-ionized water to about 9 mg/ml solids.

DETD (ii) Two formulations of 6.3 ml glycine/HSA (I) in PB plus 0.4 ml **adenovirus** solution were prepared (29 mg/ml solids, 6.3.times.10.sup.7 iu/ml). One of the formulations was diluted with de-ionized water to 9 mg/ml. . .

DETD (iii) Two formulations of 4.1 ml mannitol/glycine/HSA in PB plus 0.4 ml of **virus** solution were prepared (45.1 mg/ml solids, 8.89.times.10.sup.7 iu/ml). One of the samples was diluted with de-ionized water to 9 mg/ml. The **adenovirus** solution was freshly made on the same day and was kept cold on ice.

DETD Four formulations were prepared, two contained 25 ml of glycine/HSA (II) in PB plus 0.4 ml of **adenovirus** solution (10.5 mg/ml, 1.6.times.10.sup.7 iu/ml) and the other two contained 25 ml of glycine/HSA (II) in water plus 0.4 ml of **adenovirus** solution (8.6 mg/ml, 1.6.times.10.sup.7 iu/ml). The **adenovirus** solution underwent only one freeze/thaw cycle before usage in the above preparations. It was prepared around 10 weeks ago and. . .

DETD . . . powder was kept refrigerated and was sent for testing on dry ice. Prior to testing for .beta.-gal expression or for **virus** titers, the powders were reconstituted with phosphate buffered saline (PBS).

DETD . . . formulations of set one showed any .beta.-gal expression in the standard 6-well test and therefore they were not titered for **virus** infectivity.

DETD The glycine/HSA (I) and glycine/mannitol/HSA in PB from set one were equal in their .beta.-gal expression and were tittered for **virus** infectivity. Their titers ranged from 7% to 15% of the expected values. The particle size distribution (HORIBA), dispersibility and the. . .

DETD Set two powders and 0.1 ml of the **adenovirus** solution (V) frozen to -70.degree. C. were sent on dry ice for titer measurements (Table 4). Powders manufactured with and without the phosphate buffer retained 76-54% and 2-1.4% of their **virus** infectivities, respectively (Table 4). Lowering the outlet temperature by 5.degree. C. increased the buffered formulation **virus** infectivity by 22% but it lowered the unbuffered one by 6%.

DETD TABLE 3

Characterization of Set One Powders:
Glycine/HSA in PB **adenovirus** formulations.

Formula (mg/ml)	Dipersi. (% RSD)	HORIBA MMD	Cascade impactor MMAD	% < 5 .mu.m	% infectivity retained
29	40 (25)	2.6	2.8. . .		

DETD TABLE 3

Characterization of Set One Powders:
Glycine/HSA in PB **adenovirus** formulations.

Formula (mg/ml)	Dipersi. (% RSD)	HORIBA MMD	Cascade impactor MMAD	% < 5 .mu.m	% infectivity retained
29	40 (25)	2.6	2.8. . .		

DETD To summarize the representative results described in the above Examples, respirable dry powder aerosols containing lipid:DNA complexes or **adenovirus** vectors for the delivery of active genes to mammalian cells were prepared and tested. Dispersible dry powders containing either vehicles (i.e., lipid or **viral** vectors) were made with mannitol and/or glycine as bulking agents and HSA as a surface modifier to help disperse the powders. Transfection activities in CFT1 cells (cells from the airways of cystic fibrosis patients) and **virus** titers of the resulting powders were measured and compared to liquid

controls. The dispersibilities and aerodynamic particle size distributions of. . . formulations. Lipids and DNA were complexed with each other at least 15 minutes prior to cytofection. The titers of the **virus** in the best powder formulation and its liquid control were 76% and 16% of the expected values, respectively. The dispersibility. . . respectively. These data demonstrate the ability to obtain respirable and stable dry powder formulations of both cationic lipids complexes and **adenovirus** delivery systems.

IT 4004-05-1D, complexes with DNA 104162-48-3D, complexes with DNA **153312-64-2D**, complexes with DNA
(compns. and methods for nucleic acid delivery to lungs in gene therapy)

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=> d ibib abs hitstr 4

L50  ANSWER 4 OF 9  USPATFULL
ACCESSION NUMBER:        2001:86131  USPATFULL
TITLE:                   Non-ligand polypeptide and liposome complexes as
                         intracellular delivery vehicles
INVENTOR(S):             Duzgunes, Nejat, 508 Pixie Trail, Mill Valley, CA,
                         United States  94941
                         Simoes, Sergio, Rua Henrique Seco 33 Esq., 3000
                         Coimbra, Portugal
                         Slepushkin, Vladimir, 2013 10th St. Ct., Coralville,
                         IA, United States  52241
                         Pedras de Lima, Maria C., Rua Padre Americo 42, 4 Esq.,
                         3000 Coimbra, Portugal

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6245427          B1   20010612
APPLICATION INFO.:       US 1998-111265           19980706  (9)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            GRANTED
PRIMARY EXAMINER:        Brusca, John S.
LEGAL REPRESENTATIVE:    Dolberg, Esq., David
NUMBER OF CLAIMS:        41
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT:              999
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       The present invention discloses compositions and methods of using
         intracellular delivery vehicles for delivery and transfection of DNA,
         RNA, polypeptides, genes, proteins, drugs and biologically active agents
         into cells in vitro and in vivo. The vehicle comprises a mixture of a
         liposome and a polypeptide lacking specificity for cellular receptors.
         In another embodiment, a method for intracellular delivery of
         biologically active agents comprising combining a non-receptor-binding
         protein and a liposome, incubating the mixture for a period of time,
         adding the biologically active agent, incubating again, and finally,
         introducing the resulting mixture to the cell. Preferably, the liposome
         is a cationic liposome. The charge ratio of cationic liposome to DNA can
         effectively be varied from 2:1 to 1:2. Preferably, the
         non-receptor-binding protein is the serum albumin of the animal source
         of the cell to be transfected. This inention is an improvement over, and
         offers several advantages compared to, previously disclosed cationic
         liposomal delivery vehicles which utilize receptor ligands.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT   153312-64-2, Dmrie
          (non-ligand polypeptide and liposome complexes as intracellular
          delivery vehicles)
RN   153312-64-2  USPATFULL
CN   1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-,
       bromide (9CI)  (CA INDEX NAME)
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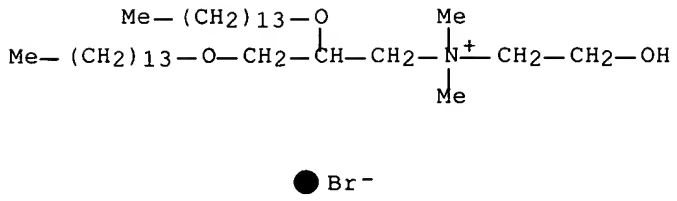

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L50 ANSWER 4 OF 9 USPATFULL

SUMM . . . of gene therapy is the effective delivery of the therapeutic agent into target cells in vitro or in vivo. Although **viral** vectors have certain advantages, including high levels of transfection, or efficient and stable integration of foreign DNA into a wide. . . of the exogenous DNA, random integration into the host genome, and the risks of inducing tumorigenic mutations and/or generating active **viral** particles through recombination (Singhal, A. and Huang, L., (1994) In: Wolf, J. A.(ed), Gene Therapeutics: Methods and Applications of Direct Gene Transfer. Birkhauser: Boston, pp118-142: Lee, R. J., and L. Huang, (1996) J. Biol. Chem. 271:8481-8487). These limitations of **viral** vectors have prompted investigators to try to improve methods of non-**viral** gene delivery. (Treco, D. A. and R. F. Selden, (1995) Mol. Med. Today 1:314-321).

SUMM Cationic liposomes have been used extensively for in vitro and in vivo gene delivery, and constitute a viable alternative to **viral** gene delivery vehicles. (Singhal A., and L. Huang, supra; Hug P and R. G. Sleight, (1991) Biochim Biophys Acta 1097:. . .

SUMM . . . from endosomes, thus preventing its lysosomal degradation and therefore enhancing transfection. Two different synthetic fusogenic peptides, "GALA" and the influenza **virus** hemagglutinin HA2 N-terminal peptide (hereinafter, "HA-2"), both low pH-activated rrtmbrane-active peptides, were used for that purpose (Simoes, S. et al.(1998). . .

SUMM It is an object of this invention to provide carriers that do not include **viral** components.

DETD . . . development of systems capable of carrying and delivering transgenes to the desired target cells. Potential problems with the use of **viral** vectors, including their immunogenicity and pathogenicity, necessitate the development of non-**viral** vectors for gene delivery. The efficiency of gene transfer mediated by lipid-based gene delivery systems, namely cationic liposomes, is limited. . .

DETD . . . in the instant invention include generally serum albumins or polypeptide fragments of serum albumins--including but not limited to human, bovine, **porcine**, murine and the like. Other useful polypeptides lacking specificity for cell receptors include, but are not limited to, apotransferrin.

DETD . . . AS A FUNCTION OF THE AMOUNT OF HUMAN SERUM ALBUMIN ASSOCIATED WITH LIPOPLEXES. The limited efficiency of transfection mediated by non-**viral** vectors, especially when compared to that by **viral** vectors, is one of the main restrictions to the more frequent use of these systems in gene therapy. In an. . .

DETD . . . cellular immunotherapy based on the use of genetically modified T-cells represents a promising strategy to increase the immune response against **viral** infections and malignant diseases, as well as to

correct single gene defects in T-cell immunodeficiency syndromes (adenosine deaminase deficiency) (Heslop,. . . 1000-1009. CD4-positive T-lymphocytes are one of the predominant cell reservoirs for HIV-1. "Intracellular immunization" of these cells, aiming at inhibiting **viral** replication, has been pursued by introduction of therapeutic genes whose expression would lead to suppression of HIV integration, to inhibition of **proviral** gene expression (Yu, M., et al., Gene Ther. (1994) 1: 13-26: Konopka K, et al., J. Drug Targeting (1998, in. . .

CLM What is claimed is:

. . . of claim 9 wherein said non-receptor-binding protein is selected from the group consisting of human serum albumin, bovine serum albumin, **porcine** serum albumin, murine serum albumin, and apotransferrin.

. . . 29 wherein said non-receptor-binding polypeptide is a protein selected from the group consisting of: human serum albumin, bovine serum albumin, **porcine** serum albumin, murine serum albumin, and apotransferrin.

IT 57-88-5, Cholesterol, biological studies 2462-63-7, Dioleoylphosphatidylethanolamine 104162-48-3, Dotma 113669-21-9, 1-Propanaminium, N,N,N-trimethyl-2,3-bis[[(9Z)-1-oxo-9-octadecenyl]oxy]- 144189-73-1, Dotap **153312-64-2**, Dmrie 165467-64-1, Dori 168479-03-6, DOSPA 168832-93-7
(non-ligand polypeptide and liposome complexes as intracellular delivery vehicles)

=> d ibib abs hitstr 5

L50 ANSWER 5 OF 9 USPATFULL
ACCESSION NUMBER: 2000:167491 USPATFULL
TITLE: X-ray guided drug delivery
INVENTOR(S): Hallahan, Dennis E., Nashville, TN, United States
PATENT ASSIGNEE(S): Vanderbilt University, Nashville, TN, United States (U.S. corporation)

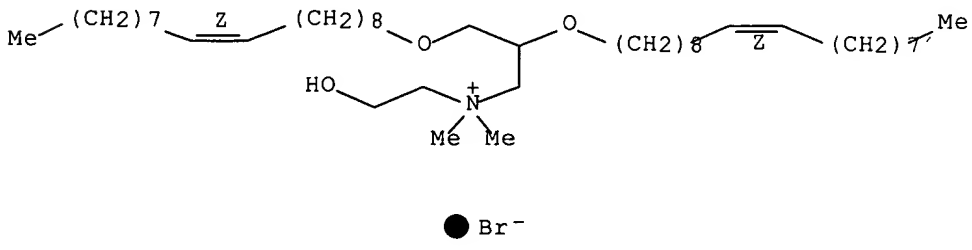
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6159443		20001212
APPLICATION INFO.:	US 1999-302456		19990429 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Sandals, William
LEGAL REPRESENTATIVE: Jenkins & Wilson, P.A.
NUMBER OF CLAIMS: 104
EXEMPLARY CLAIM: 1
LINE COUNT: 2916
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of delivering an active agent to a target tissue, particularly neoplastic tissue, vascular anomaly or tumor tissue, in a vertebrate subject. The method includes the steps of exposing the target tissue to ionizing radiation; and administering a delivery vehicle to the vertebrate subject before, after, during, or combinations thereof, exposing the target tissue to the ionizing radiation. The delivery vehicle includes the active agent and delivers the agent to the target tissue. Exemplary delivery vehicles include platelets; leukocytes; proteins or peptides which bind activated platelets; antibodies which bind activated platelets; microspheres coated with proteins or peptides which bind activated platelets; liposomes conjugated to platelets, leukocytes, proteins or peptides which bind activated platelets, or antibodies which bind activated platelets; and combinations thereof.

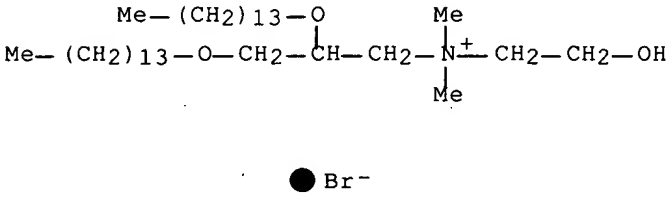
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153312-60-8**, DORIE
(SNAP 5114; X-ray guided drug delivery)
RN 153312-60-8 USPATFULL
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis[(9Z)-9-octadecenyloxy]-, bromide (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **153312-64-2**, Dmrie
(X-ray guided drug delivery)

RN 153312-64-2 USPATFULL
CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d kwic 5

L50 ANSWER 5 OF 9 USPATFULL
SUMM AcNPV--Autograph californica nuclear polyhidrosis **virus**
SUMM CaMV--Cauliflower mosaic **virus**
SUMM PAP--pokeweed **antiviral** protein
SUMM RSVE--reconstituted Sendai **virus** envelopes
SUMM TMV--Tobacco mosaic **virus**
SUMM Currently practiced methods of tumor specific drug delivery involve the use of antibody conjugates to liposomes and **viral** vectors. These methods are specific for tumor subtype or are nonspecific in localization. These limitations are significant in that, on. . .
SUMM . . . preparation of loaded blood platelets which include a loading vehicle selected from the group consisting of liposomes and reconstituted Sendai **virus** envelopes. A diagnostic or therapeutic agent is encapsulated within the loading vehicle. However, there is no disclosure of a targeting. . .
SUMM . . . within or on a wide variety of hosts; for example, human hosts, canine hosts, feline hosts, equine hosts, bovine hosts, **porcine** hosts, and the like. Any host in which is found a neoplasm or neoplastic cells can be treated and is. . .
SUMM . . . include sites which bind activated platelets and which bind an active agent, such as a gene therapy vector, preferably a **viral** gene therapy vector. Preferred antibodies comprise anti-P-selectin, anti-GP-IIb, and anti-GP-IIIa antibodies.
SUMM . . . Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing delivery vehicle/active agent coding sequences; insect cell systems infected with recombinant **virus** expression vectors (e.g., **baculovirus**) containing the delivery vehicle/active agent coding sequences; plant cell systems infected with recombinant **virus** expression vectors (e.g., cauliflower mosaic **virus**, CaMV; tobacco mosaic **virus**, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing the delivery vehicle/active agent coding sequences coding sequence;. . . expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the **adenovirus** late promoter; the vaccinia **virus** 7.5K promoter; **lentiviral** vectors).
SUMM In an insect system, Autograph californica nuclear polyhidrosis **virus** (AcNPV) is used as a vector to express foreign genes. The **virus** grows in Spodoptera frugiperda cells. The delivery vehicle/active agent coding sequences may be cloned into non-essential

regions (for example the polyhedrin gene) of the **virus** and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of the delivery vehicle/active agent coding sequences will result in inactivation of the polyhedrin gene and production of non-occluded recombinant **virus** (i.e., **virus** lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect Spodoptera frugiperda. . .

SUMM In mammalian host cells, a number of **viral** based expression systems may be utilized. In cases where an **adenovirus** is used as an expression vector, the delivery vehicle/active agent coding sequences may be ligated to an **adenovirus** transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the **adenovirus** genome by in vitro or in vivo recombination. Insertion in a non-essential region of the **viral** genome (e.g., region E1 or E3) will result in a recombinant **virus** that is viable and capable of expressing delivery vehicle/active agent proteins in infected hosts (see e.g., Logan et al., Proc.. . .

SUMM . . . which stably express constructs encoding the delivery vehicle/active agent compounds may be engineered. Rather than using expression vectors which contain **viral** origins of replication, host cells can be transformed with delivery vehicle/active agent DNA controlled by appropriate expression control elements (e.g.,. . .

SUMM A number of selection systems may be used, including, but not limited, to the herpes simplex **virus** thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoriboxyltransferase (Szybalska et al., Proc. Natl. Acad. Sci. USA 48:2026 (1962)),. . .

SUMM . . . by electroporation or by phagocytosis, membrane fusion or receptor-mediated endocytosis. For example, leukocytes can be loaded by conjugating with a **viral** gene therapy vector to a platelet binding P-selectin counter receptor (PGSL) on the surface of the leukocyte using the conjugation. . .

SUMM . . . not limited to: ricin, ricin A chain (ricin toxin), Pseudomonas exotoxin (PE), diphtheria toxin (DT), bovine pancreatic ribonuclease (BPR), pokeweed **antiviral** protein (PAP), abrin, abrin A chain (abrin toxin), gelonin (GEL), saporin (SAP), modeccin, viscumin and volkensin.

SUMM . . . kept as pets or in zoos) to humans, for instance, carnivores other than humans (such as cats and dogs), swine (**pigs**, hogs, and wild boars), ruminants (such as cattle, oxen, sheep, giraffes, deer, goats, bison, and camels), and horses. Also contemplated. . . also of economical importance to humans. Thus, contemplated is the treatment of livestock, including, but not limited to, domesticated swine (**pigs** and hogs), ruminants, horses, poultry, and the like.

DETD Platelets are also loaded using the open channel system (OCS), receptor-mediated endocytosis using retention of liposomes, or reconstituted Sendai **virus** envelopes (RSVE). These techniques have been used to load chemotherapeutic agents such as adrimycin, cis-platinum and radioisotopes. Platelets are loaded. . .

CLM What is claimed is:

. . . Factor X, thrombin, phospholipase C, cobra venom factor, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, bovine pancreatic ribonuclease, pokeweed **antiviral** protein, abrin, abrin A chain, gelonin, saporin, modeccin, viscumin, volkensin and combinations thereof.

34. The method of claim 33, wherein the genetic construct further comprises a **viral** vector.

. . . Factor X, thrombin, phospholipase C, cobra venom factor, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, bovine pancreatic ribonuclease, pokeweed **antiviral** protein, abrin, abrin A chain, gelonin, saporin, modeccin, viscumin, volkensin and combinations thereof.

71. The method of claim 70, wherein the genetic construct further comprises a **viral** vector.

IT **153312-60-8**, DORIE
(SNAP 5114; X-ray guided drug delivery)
IT 57-88-5, Cholesterol, biological studies 2462-63-7, Dope 9003-09-2, Polyvinylmethylether 9003-39-8, Polyvinylpyrrolidone 9004-62-0, Hydroxyethylcellulose 14357-21-2 25014-12-4, Polymethacrylamide 25322-68-3, Polyethyleneglycol 25805-17-8, Polyethyloxazoline 26375-28-0 37353-59-6, Hydroxymethylcellulose 104162-48-3, Dotma 113669-21-9 137056-72-5, Dc-chol **153312-64-2**, Dmrie 158606-68-9, Polyaspartamide 306284-11-7 306284-12-8
(X-ray guided drug delivery)

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=> d ibib abs hitstr 6

L50  ANSWER 6 OF 9  USPATFULL
ACCESSION NUMBER:        2000:150136  USPATFULL
TITLE:                   Liposomal peptide-lipid conjugates and delivery using
                         same
INVENTOR(S):             Meers, Paul R., Princeton Junction, NJ, United States
                         Pak, Charles, Plainsboro, NJ, United States
                         Ali, Shaukat, Monmouth Junction, NJ, United States
                         Janoff, Andrew, Yardley, PA, United States
                         Franklin, J. Craig, East Windsor, NJ, United States
                         Erukulla, Ravi K., Plainsboro, NJ, United States
                         Cabral-Lilly, Donna, Lawrenceville, NJ, United States
PATENT ASSIGNEE(S):      The Liposome Company, Inc., Princeton, NJ, United
                         States (U.S. corporation)

                              NUMBER       KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6143716               20001107
APPLICATION INFO.:       US 1998-168010           19981007  (9)
RELATED APPLN. INFO.:    Division of Ser. No. US 1997-950618, filed on 15 Oct
                         1997

                                NUMBER         DATE
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PRIORITY INFORMATION:    US 1996-27544      19961015 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            Granted
PRIMARY EXAMINER:        Moezie, F. T.
LEGAL REPRESENTATIVE:    Goodman, Rosanne
NUMBER OF CLAIMS:        14
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      19 Drawing Figure(s); 16 Drawing Page(s)
LINE COUNT:              1650
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Peptide-lipid conjugates are incorporated into liposomes so as to
       selectively destabilize the liposomes in the vicinity of target
       peptidase-secreting cells, and hence, to deliver the liposomes to the
       vicinity of the target cells, or directly into the cells. The liposomes
       can thus be used to treat mammals for diseases, disorders or conditions,
       e.g., tumors, microbial infection and inflammations, characterized by
       the occurrence of peptidase-secreting cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT  153312-64-2, Dmrie
       (peptide-lipid conjugates for liposomal drug delivery)
RN   153312-64-2  USPATFULL
CN   1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-,
       bromide (9CI)  (CA INDEX NAME)
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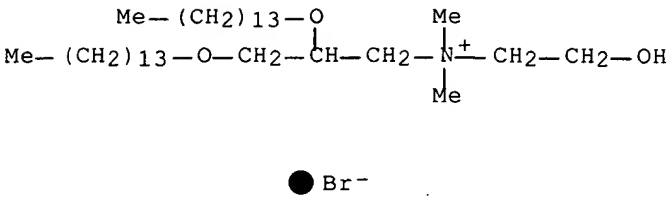

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L50  ANSWER 7 OF 9  USPATFULL
ACCESSION NUMBER:        2000:88154  USPATFULL
TITLE:                   Peptide-lipid conjugates
INVENTOR(S):             Meers, Paul R., Princeton Junction, NJ, United States
                         Pak, Charles, Plainsboro, NJ, United States
                         Ali, Shaukat, Monmouth Junction, NJ, United States
                         Janoff, Andrew, Yardley, PA, United States
                         Franklin, J. Craig, East Windsor, NJ, United States
                         Erukulla, Ravi K., Plainsboro, NJ, United States
                         Cabral-Lilly, Donna, Lawrenceville, NJ, United States
PATENT ASSIGNEE(S):      The Liposome Company, Inc., Princeton, NJ, United
                         States (U.S. corporation)

                              NUMBER        KIND    DATE
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PATENT INFORMATION:      US 6087325                20000711
APPLICATION INFO.:       US 1997-950618            19971015  (8)

                              NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 1996-27544      19961015 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            Granted
PRIMARY EXAMINER:        Davenport, Avis M.
LEGAL REPRESENTATIVE:    Goodman, Rosanne
NUMBER OF CLAIMS:        12
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      11 Drawing Figure(s); 16 Drawing Page(s)
LINE COUNT:              1600
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     Peptide-lipid conjugates are incorporated into liposomes so as to
       selectively destabilize the liposomes in the vicinity of target
       peptidase-secreting cells, and hence, to deliver the liposomes to the
       vicinity of the target cells, or directly into the cells. The liposomes
       can thus be used to treat mammals for diseases, disorders or conditions,
       e.g., tumors, microbial infection and inflammations, characterized by
       the occurrence of peptidase-secreting cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT  153312-64-2, Dmrie
       (peptide-lipid conjugates for liposomal drug delivery)
RN   153312-64-2  USPATFULL
CN   1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-,
       bromide (9CI)  (CA INDEX NAME)
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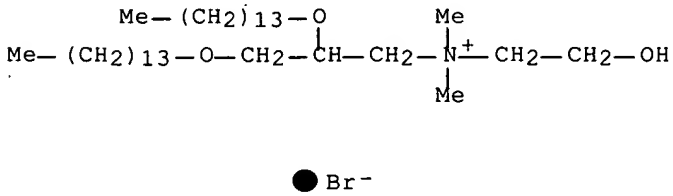

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L50 ANSWER 8 OF 9 USPATFULL

ACCESSION NUMBER:	1999:155697 USPATFULL
TITLE:	Compositions and methods for nucleic acid delivery to the lung
INVENTOR(S):	Eljamal, Mohammed, San Jose, CA, United States Patton, John S., San Carlos, CA, United States Foster, Linda, Sunnyvale, CA, United States Platz, Robert M., Half Moon Bay, CA, United States
PATENT ASSIGNEE(S):	Inhale Therapeutic Systems, Inc., San Carlos, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5994314		19991130
APPLICATION INFO.:	US 1995-422563		19950414 (8)

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1995-417507, filed on 4 Apr 1995, now abandoned which is a continuation of Ser. No. US 1993-44358, filed on 7 Apr 1993, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Elliott, George C.
ASSISTANT EXAMINER:	Larson, Thomas G.
LEGAL REPRESENTATIVE:	Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS:	27
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	832

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

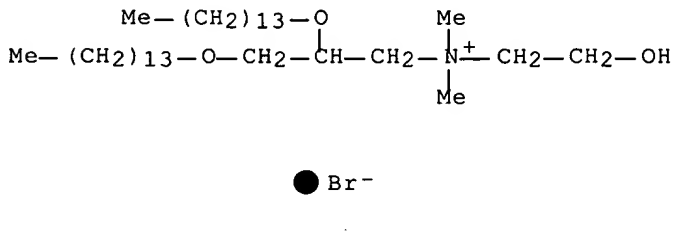
AB A dry powder composition comprises insoluble nucleic acid constructs dispersed within with a hydrophilic excipient material, where the powder particles have an average size in the range from 0.5 .mu.m to 50 .mu.m. Nucleic acid constructs may comprise bare nucleic acid molecules, **viral** vectors, or vesicle structures. The hydrophilic excipient material will be selected to stabilize the nucleic acid molecules in the constructs, enhance dispersion of the nucleic acid in dry powder aerosols, and enhance wetting of the nucleic acid constructs as they are delivered to moist target locations within the body.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **153312-64-2**, Dmrie
(dry-powder compns. and methods for nucleic acid delivery to the lung)

RN 153312-64-2 USPATFULL

CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d ibib abs hitstr 9

L50 ANSWER 9 OF 9 USPATFULL

ACCESSION NUMBER:	1999:65244 USPATFULL		
TITLE:	Plasmids suitable for gene therapy		
INVENTOR(S):	Nabel, Gary J., Ann Arbor, MI, United States Nabel, Elizabeth G., Ann Arbor, MI, United States Lew, Denise, Encinitas, CA, United States Marquet, Magda, La Jolla, CA, United States		
PATENT ASSIGNEE(S):	Vical Incorporated, San Diego, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5910488		19990608
	WO 9429469		19941222
APPLICATION INFO.:	US 1995-564313		19951201 (8)
	WO 1994-US6069		19940527
			19951201 PCT 371 date
			19951201 PCT 102(e) date
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1993-74344, filed on 7 Jun 1993, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Stanton, Brian R.		
ASSISTANT EXAMINER:	Hauda, Karen M.		
LEGAL REPRESENTATIVE:	Knobbe, Martens, Olson & Bear, LLP		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1,14,19		
LINE COUNT:	2089		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

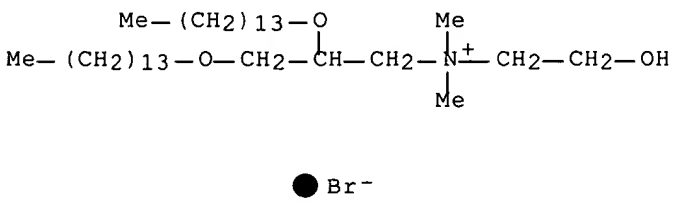
AB The invention provides vectors adapted for use in transferring into tissue or cells of an organism genetic material encoding one or more cistrons capable of expressing one or more immunogenic or therapeutic peptides and related methods.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **153312-64-2**, Dmrie
(liposomes; plasmids suitable for antitumor gene therapy)

RN 153312-64-2 USPATFULL

CN 1-Propanaminium, N-(2-hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-, bromide (9CI) (CA INDEX NAME)



=> d kwic 9

L50 ANSWER 9 OF 9 USPATFULL

SUMM . . . in an effort to treat malignancy. This protocol proposed to perform direct gene transfer in humans and to utilize a non-**viral** vector which reduces several safety concerns about **viral** vectors. This clinical trial involved the treatment of patients with metastatic melanoma at subcutaneous lesions. The treatment constituted intratumoral injection. . .

SUMM . . . molecule, a foreign major histocompatibility complex (MHC), was used to elicit an immune response in the iliofemoral artery using a **porcine** model. The human HLA-B7 gene was introduced using direct gene transfer with a **retroviral** vector or DNA liposome complex (E. G. Nabel, et al., Proc. Natl. Acad. Sci. USA 89, 5157 (1992)). With either. . .

SUMM . . . MHC gene into established human tumors (supra). The antigenicity of tumor cells had been altered previously by the expression of **viral** antigens through infection of tumor cells (J. Lindenmann and P. A. Klein, J. Exp. Med. 126, 93 (1967); Y. Shimizu,. . .

SUMM . . . binding site that facilitates translation of messages of any of the cistrons, which ribosome binding site is derived from EMC **virus**; translation initiation sequence that facilitates expression of any of the cistrons; and genetic material that facilitates splicing of transcripts of. . .

SUMM . . . lipid formulation may be DMRIE-DOPE. The DMRIE-DOPE may have a molar ratio of 5:5. The vehicle may comprise an infection-facilitating **viral** vector.

SUMM . . . lipid formulation may be DMRIE-DOPE. The DMRIE-DOPE may have a molar ratio of 5:5. The vehicle may comprise an infection-facilitating **viral** vector.

SUMM . . . binding site that facilitates translation of messages of any of the cistrons, which ribosome binding site is derived from EMC **virus**; translation initiation sequence that facilitates expression of any of the cistrons; and genetic material that facilitates splicing of transcripts of. . .

SUMM . . . of messages of any of the cistrons internal to the transcription unit which ribosome binding site is derived from EMC **virus**; translation initiation sequence that facilitates expression of any of the cistrons; and intron sequence that facilitates splicing of transcripts of. . .

SUMM . . . preferred embodiment, they are derived from bacterial plasmids. Plasmid vectors are likely to be at least as safe as standard **viral** vectors, as they will not be introduced into a packaging cell line thus precluding incorporation of other recombinant gene products. . .

SUMM . . . interact with eukaryotic RNA polymerases. Such promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from **retrovirus**, and mouse metallothionein-I. CMV and Rous Sarcoma **Virus** long terminal repeat (RSV LTR) are preferred.

SUMM . . . is a problem. For polycistronic plasmids, it is preferred, therefore, that the ribosome binding site be derived from encephalomyocarditis (EMC) **virus**. This site is incorporated into the vector where it can function as an internal entry point for initiation of translation. . .

SUMM . . . positive determinants of mRNA stability are also provided, which determininants preferably constitute poly A addition sequences. Polyadenylation sites derived from non-**viral** sources are preferred to avoid contamination with **viral** gene products; for example, bovine growth hormone gene derived poly A addition sequence is preferred. Also expressly contemplated and preferred are **viral**

sources of poly A signals, such as SV40, where essentially all of any open reading frames encoding **viral** proteins contained therein have been deleted.

SUMM . . . intron is derived from SV40, wherein essentially all of any open reading frames have been deleted to obviate contamination with **viral** gene products. In this same regard, vectors may also be optimized by deletion of introns. In a preferred embodiment of. . .

SUMM . . . proteins via a bi-cistronic mRNA in eukaryotic cells. Initiation of transcription of the mRNA is dependent on a Rous Sarcoma **Virus** promoter sequence derived from the 3' Long Terminal Repeat. Termination of transcription is dependent upon the polyadenylation signal sequence derived. . . site. Translation of the light chain is controlled by a Cap Independent Translational Enhancer (CITE) sequence derived from the Encephalomyocarditis **Virus**. Finally, replication of the plasmid in bacterial cells is controlled by the presence of a bacterial origin of replication. There. . .

SUMM Eukaryotic gene expression is regulated by the Avian Rous Sarcoma **Virus** (RSV) 3' Long Terminal Repeat (LTR) promoter sequence. This sequence was derived from the Schmidt-Ruppin strain of RSV (Swanstrom, R.,. . . Nat'l Acad. Sci. U.S.A. 78, 124 (1981)) and was cloned by isolating DNA bounded by the Pvu II site at **viral** base number 8673 and the Bfa I site at **viral** base number 9146. The use of this promoter sequence to regulate the expression of heterologous genes in eukaryotic cells was. . . from the pRSV.beta.-globin (Gorman, C., et al., Science 221, 551 (1983)). Although this regulatory sequence is found in an avian **retrovirus**, this 3' LTR has been tested and shown to have no intrinsic oncogenic activity in either avian or mammalian cells. . .

SUMM . . . HLA-B7) and CAP independent (.beta.-2 microglobulin) ribosome recognition sequences. The CAP independent signal is taken from the murine encephalomyocarditis (EMC) **virus** genome and is cloned between the HLA-B7 heavy and light chains coding sequences and as part of the bicistronic mRNA.

SUMM . . . or tissues of organisms may be accomplished by injecting naked DNA or facilitated by using vehicles, such as, for example, **viral** vectors, ligand-DNA conjugates, **adenovirus** -ligand-DNA conjugates, calcium phosphate, and liposomes. Transfer procedures are art-known, such as, for example, transfection methods using liposomes and infection protocols using **viral** vectors, including **retrovirus** vectors, **adenovirus** vectors, adeno-associated **virus** vectors, herpes **virus** vectors, vaccinia **virus** vectors, polio **virus** vectors, and sindbis and other RNA **virus** vectors.

DETD . . . to permit translation of the second message. Towards this end, a fragment containing such a site derived from encephalomyocarditis (EMC) **virus** was removed from pCITE-1, procured from Novagen (Madison, Wis.), by digestion with Eco RI and Xba I. The fragment was. . .

DETD . . . derived from pBR322, a bi-cistronic transcription unit under the control of a single promoter, a promoter derived from Rous sarcoma **virus** long terminal repeat (RSV-LTR) in which a poly A site had been mutated, an internal ribosome initiation site, consensus translation. . .

DETD . . . SV40 sequences, from 1612 bp to 384 bp, was engineered. Deletions removed two open reading frames encoding portions of SV40 **viral** proteins, the small t antigen and VPI.

DETD . . . was originally cloned as a 993 base pair fragment from a Bcl I to Eco RI site from the SV40 **viral** genome. Extraneous sequences in this region coded for a **viral** structural protein, VPI. Elimination of extraneous regions of the SV40 polyadenylation

signal was accomplished by deleting a 757 bp fragment. . .

DETD . . . by the use of a kanamycin selectable marker. Importantly, the eradication of two open reading frames encoding portions of SV40 **viral** proteins lowers the risk of tumorigenicity. The vector may also operate as a cassette into which cistrons may be inserted. . .

DETD . . . intratumor injections. In addition, one might also examine the response to is foreign MHC gene expression in the model using **porcine** arteries in vivo (E. G. Nabel, et al., Proc. Natl. Acad. Sci. USA 89, 5157 (1992)).

DETD . . . injection into the end artery which perfuses an isolated nodule is used with an occlusion balloon catheter. In murine and **porcine** models, the highest treatment exceeded these proposed doses by 100-fold and are well-tolerated. Doses are repeated within each subject for. . .

DETD . . . weeks prior to the initial treatment, a blood sample is obtained to derive lymphocytes which are immortalized using the Epstein-Barr **virus**. An aliquot of these cells are further infected with an amphotropic HLA-B7 **retroviral** vector, and expression is confirmed on the cell surface. These cells are subsequently used in the laboratory as target cells. . .

IT 2462-63-7, Dope **153312-64-2**, Dmrie
(liposomes; plasmids suitable for antitumor gene therapy)

US 095865350YP1

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No.	Doccode	Number of pages
1	NPL	2
2	NPL	2
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Total number of pages: 123

Remarks:

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